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MALIGNANT MELANOMA IN KENTUCKY: AN ANALYSIS OF THE INDIVIDUAL AND SOCIAL FACTORS ON DISEASE STAGE AND TREATMENT

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ABSTRACT OF CAPSTONE

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The College of Public Health

University of Kentucky

2017

MALIGNANT MELANOMA IN KENTUCKY: AN ANALYSIS OF THE INDIVIDUAL AND SOCIAL FACTORS ON DISEASE STAGE AND TREATMENT

ABSTRACT OF CAPSTONE

A Capstone project submitted in partial fulfillment of the requirements for the degree of Doctor of Public Health in the College of Public Health
at the University of Kentucky

By:

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ABSTRACT OF CAPSTONE

MALIGNANT MELANOMA IN KENTUCKY: AN ANALYSIS OF INDIVIDUAL AND SOCIAL FACTORS ON DISEASE STAGE AND TREATMENT

Introduction: In 2016 there will be an estimated 76,380 new cases of malignant melanoma and 10,130 deaths in the United States (US). [1] Malignant melanoma incidence is increasing faster than any other preventable cancer in the US with an expected 112,000 new cases a year by 2030. [2,3] This capstone attempts to quantify the association of individual and social factors on melanoma late-stage diagnosis and non-adherence to surgical treatment guidelines for early-stage lesions in Kentucky.

Methods: The analysis combines three datasets: individual level data from the Kentucky Cancer Registry, census tract level data from the US Census and county level physician licensure data from the Kentucky Department of Public Health. Descriptive statistics, univariate and multivariate logistic regression analyses were completed.

Results: The first paper hypothesized that late-stage diagnosis is associated with an increase in poverty level, decrease in education level and decrease in physician density. An association between these variables of interest were not found, rather, this study supports previous research that there is decreased odds of late-stage diagnosis if female, married and carry private insurance. [65,123,125]

The second paper hypothesized that non-standard treatment more frequently occurs in rural and Appalachian regions and geographic areas with lower physician density and lower socioeconomic status as indicated by an increase in poverty level and decrease in education level. An association between non-standard treatment and Appalachian geography, poverty level and physician density was found. Non-standard treatment was provided to 40% of early-stage cases and this rate is rising.

Conclusions: Kentucky is a rural state with high poverty, lower than average education levels and low physician density but it appears that these factors have not impacted melanoma stage of diagnosis. Instead, policy implementation should focus on the need to increase patient access to melanoma care and educating clinicians to halt the trend of increasing non-standard melanoma surgical treatment for early-stage lesions in the Commonwealth.

KEYWORDS: malignant melanoma; stage of diagnosis; socioeconomic status; Appalachian; treatment guidelines

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

PAGE

CHAPTER IV

CHAPTER I

Introduction

In 2016 there will be an estimated 76,380 new cases of malignant melanoma and 10,130 deaths in the United States (US). [1] Malignant melanoma (here forward referred to as melanoma) incidence is increasing faster than any other preventable cancer in the US with an expected 112,000 new cases a year by 2030. [2,3] This is a public health concern because as rates steadily rise there is no universal screening recommendation. [4,5]

Melanoma is an intriguing disease; unlike other forms of cancer the incidence occurs in a positive social gradient, where those with a higher socioeconomic status (SES) have the highest incidence. Meanwhile those with low SES have higher rates of late-stage disease and higher mortality rates.[6] These findings have led to an interest in further delineating the characteristics of those people who have melanoma by disease stage and how their disease is treated.

As more than 90% of all US melanoma lesions develop in non-Hispanic whites, Kentucky makes an interesting place to study this disease because 89% of the population is white with an above average poverty rate of 19%. [7,8] Kentucky also has a higher rate of melanoma compared to the US with a survey noting that some counties such as Russell and Warren ranking among the highest in the country. [9] Additionally, as the increasing mortality rate from melanoma leveled off in the US in the late 1980s the level has continued to rise in Kentucky. [10] There may be several factors, individual and/or social, in

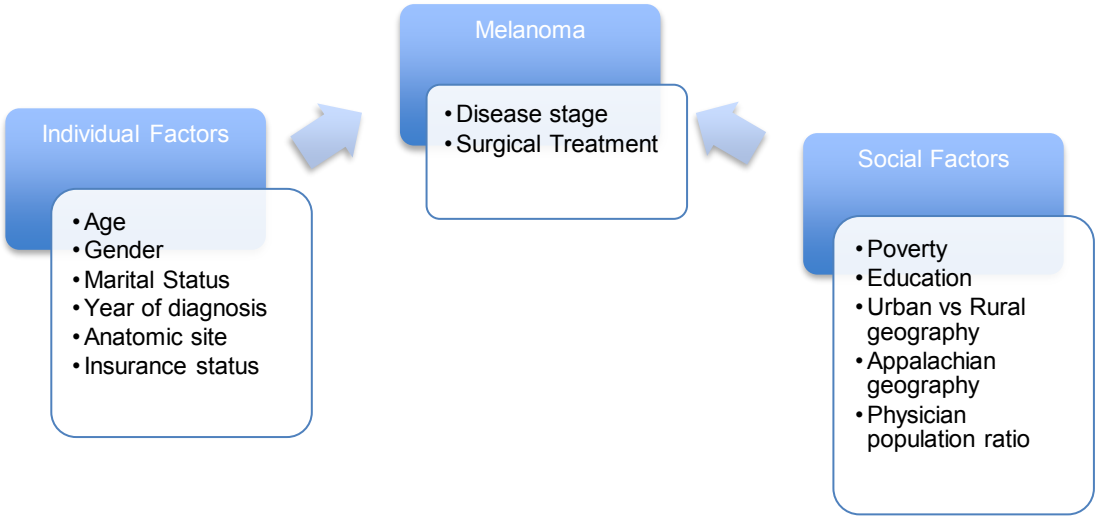
Kentucky that are impacting melanoma incidence and mortality as the Commonwealth has a higher proportion of the population which is generally impoverished, rural, and medically underserved compared to other states. [8,11,12]

Studies have shown that melanoma disease stage and treatment is influenced by both individual and social factors. These factors include age, gender, race, ultraviolet radiation (UVR) exposure, SES, marital status, geographic location, tumor histology, tumor location, insurance status, access to health care, and prevention efforts of sun-protective behaviors, risk awareness and early detection efforts. [7,13-25] Additionally, the stage of diagnosis and receiving appropriate treatment for that stage directly impacts melanoma survival. [26,27] Despite specific treatment guidelines from the National Comprehensive Cancer Network (NCCN) the evidence suggests that these melanoma surgical guidelines are not followed half of the time. [28]

Purpose of the study

The purpose of this capstone is to understand the variables leading to late-stage disease diagnosis and the high mortality rate in Kentucky. This will be done through a logistic regression analysis of individual and social factors on melanoma stage of diagnosis and surgical treatment provided.

Figure 1.1, Flow Diagram of Malignant Melanoma and Individual and Social Factors with Possible Association with Disease Stage and Treatment



This capstone will include two papers, which will quantify the association of individual and social factors on melanoma late-stage diagnosis and non-adherence to surgical treatment guidelines for early-stage lesions in Kentucky. Refer to figure 1.1. The hope is that by determining the factors that are attributing to late-stage diagnosis and surgical treatment guideline non-adherence for early-stage lesions that an area for direct public health intervention will be uncovered. Paper one will describe the incidence and mortality rates of malignant melanoma in white non-Hispanic Kentuckians from 1995 to 2013. Then the association of individual and social variables (age, gender, marital status, year of diagnosis, anatomical site of lesion, health insurance status, urban/rural geography, Appalachian/non-Appalachian geography, poverty level, education level and

physician population ratio) on incidence rates of all cases, early-stage and late-stage melanoma, in white non-Hispanic Kentuckians from 1995 to 2013 will be quantified.

Paper two will report the percentage of cases with early-stage disease that did not adhere to the standard of care treatment, defined as clear margins, in white non-Hispanic Kentuckians from 1995 to 2013. Then the association of individual and social variables (age, gender, marital status, year of diagnosis, anatomical site of lesion, health insurance status, urban/rural geography, Appalachian/non-Appalachian geography, poverty level, education level and physician population ratio) on the treatment provided to early-stage melanoma cases in white non-Hispanic Kentuckians from 1995 to 2013 will be quantified.

The high poverty rate combined with the high incidence and mortality rates of melanoma in Kentucky make this an interesting study. This study is relevant due to the continued rise in melanoma incidence with no clear public health solution. While most studies have looked at melanoma by analyzing a few variables, this study attempts to analyze both individual and social determinants. The analysis combines three datasets: individual level data from the Kentucky Cancer Registry (KCR), census tract level data from the US Census and county level physician licensure data from the Kentucky Department of Public Health.

Limitations, Delimitations, Innovations

There are some important limitations to this proposal. First, there is the utilization of community level variables for SES as individual level variables are not available. The contextual variables of poverty and education for SES will be

utilized to understand the impact of the community on melanoma stage of diagnosis and treatment. The use of aggregate measures for SES has been validated but both poverty and education contextual variables represent community level data and not individual level data. [29-31] Also, physician population ratio is used as an aggregate to evaluate health care access but we cannot know the amount of services used by the patients individually. This data is cross sectional from 2006 and may not fully represent the small variation in the physician workforce from 1995 to 2013. Additionally, this data did not account for other medical providers including physician assistants and nurse practitioners. To provide more accurate individual representation of the community level variables of poverty, education and physician density this data was provided at the county level in a state with 120 counties. Future research may better capture community level characteristics by analysis with larger geographic regions. Although this study analyzes multiple variables, melanoma subtypes are not included so the effect of this variable cannot be investigated in this study. Lastly, this study is restricted to melanoma cases in Kentucky and may not be representative of other forms of skin cancer or other regions of the country.

Several delimitations have been placed on this study. As the majority of the population in Kentucky is white non-Hispanics this will be the population studied. Therefore, the effect of race on both disease stage and treatment cannot be determined. Also, due to the low mortality rate the variables impacting survival will not be studied. Lastly, with the changes in the standard of care for surgical

and chemotherapy treatment during the time period of study, this study will only analyze surgical treatment via clear surgical margins of localized disease.

This study also offers several innovations. This analysis will be the first to provide insight into the high melanoma incidence and mortality rate in Kentucky. The study population offers an opportunity to study previously investigated factors in a rural, impoverished and lowered educated state. This analysis will also be the first to provide a regression analysis looking at individual and social determinants of non-adherence to melanoma surgical treatment guidelines in Kentucky. Additionally, this study design provides a novel methodology by evaluating if the melanoma NCCN guidelines for surgical treatment were followed in a mostly rural and Appalachian population. This evaluation of individual and social determinants will lend needed insight into the complexity of providing the standard of care surgical treatment for melanoma. The purpose of this capstone is to help guide future public health interventions for melanoma in Kentucky.

This capstone will be divided by chapters and include two separate papers with background, methods, results and discussion sections that examine two distinct facets of melanoma as described above. Chapter two will begin with a comprehensive literature review of melanoma pathophysiology, staging, treatment, incidence, prevalence, mortality, risk factors, prevention and screening recommendations. This will be followed by a detailed account of the variables that have been found to influence disease stage and surgical treatment. Following the literature review, chapter three will contain paper one which is an analysis of the individual and social variables associated with late-stage

melanoma diagnosis in the Commonwealth. Chapter four will then include paper two which is an analysis of the individual and social variables associated with non-adherence to surgical treatment provided for early-stage melanoma. Lastly, chapter five will summarize the capstone by providing further conclusions and recommendations.

CHAPTER 2

Literature review

This chapter is a literature review of melanoma pathophysiology, staging, treatment, incidence, prevalence, mortality, risk factors, prevention and screening recommendations. This will be followed by a comprehensive review of the literature on variables that have been shown to effect melanoma stage of diagnosis and adherence to surgical treatment guidelines. This review comprises the most recent and relevant research regarding melanoma. The works cited were gathered from presentations, books and peer reviewed journals. The databases used were PubMed, Scopus, Embase, Tripp, UpToDate, and MedlinePlus. Key word searches included melanoma, disease stage, treatment, treatment guidelines, incidence, mortality, socioeconomic status, poverty, education, Kentucky, and Appalachian region. Further review of the literature encompassed reviewing the US and European treatment guidelines, referencing bibliographies of seminal articles as well as those recommended by experts and colleagues.

Pathophysiology, Staging and Treatment

The largest human organ is the skin and it is the first line of protection for the human body. [32] The epidermis is the thin most superior layer of the skin and keratinocytes that provide a physicochemical barrier are the most abundant cell within the epidermis. Melanocytes are the only source of pigment in the skin and are found in both the epidermis and dermis. [33] Melanocytes can form malignant

melanoma or benign skin lesions such as moles or spitz nevus. [23,34] Keratinocytes contain most of the melanin in the skin and act as a natural sunscreen to protect the skin against ultraviolet radiation (UVR). [33] UVR sensitivity and skin complexion are determined by the amount and type of epidermal melanin. There are two types of melanin: eumelanin-- a dark pigment expressed profusely in the skin of heavily pigmented people that is protective and pheomelanin-- a light-colored pigment that is seen in fair-skinned people. This difference in melanin explains why fair-skinned people experience more UVR damage. [33]

Cancer is a dysregulation of cell division in which the cell continues to divide without limitations. Cancer cells also reproduce more rapidly and in a disorganized fashion. [35] The common types of skin cancer are squamous cell carcinoma, basal cell carcinoma and melanoma. Melanoma is considered a pigmented skin cancer that is significantly more aggressive and deadly than the other forms of skin cancer.[32] The complexity of melanoma is not fully understood yet it is now widely accepted that melanoma development occurs from interplay of genetics and exposure to UVR radiation. [36]

Continued research into UVR exposure has led to the clinical description of subtypes cutaneous melanoma: non-chronic sun damage and chronic sun-induced damage. [37] The non-chronic sun damaged lesions are noted to have a high proportion of BRAF mutations. [38] The worldwide study of families with high rates of melanoma has found genetic germline mutations in CDKN2A and CDK4.[39,40] Although important information, it is unlikely that these genetic

findings play a large role in population-based melanoma. [40] Whereas, recent findings through epigenomics, the Cancer Genome Atlas project and research into stem cells has helped to explain the role of pathways such as mitogen-activated protein, BRAF mutation, VEGFR1, CD133 and CD34. [41] As research works towards a full understanding of melanoma these findings have led to the development of promising molecular targeted therapies.

Melanoma can be found on any area of the body that has melanocytes which includes the skin, meninges, mucous membranes and eyes. [32] Melanoma is distinctive in that it can arise anywhere on the body including the palms or soles of the feet. [42] Also unique, melanocytes form lesions that are dark in appearance yet not all melanoma lesions are dark. [23,42]

Melanoma presents as one of four subtypes: superficial spreading, nodular, lentigo maligna and acral lentiginous. [32] Superficial spreading is the most common variant comprising 70% of all lesions and has a good prognosis. These lesions are dark black to red and found on the back or in women on the lower legs. Nodular lesions are the subtype with the worst prognosis and comprise 15-30% of all lesions. Nodular lesions are seen anywhere on the body with variation between black to pink lesions and have the shortest growth cycle of any subtype. Lentigo maligna lesions comprise 10-15% of all lesions and have a good prognosis. They appear tan brown and present on people over 70 years of age on the sun-exposed surfaces of the skin. Acral lentiginous lesions have a poor prognosis and are the least common subtype comprising less than 5% of all lesions. These lesions are a brown to blue color and appear on the soles, palms,

nail beds and mucous membranes. [32,43-45] Each type of lesion has distinct characteristics and growth durations yet the histopathology is not considered a distinct prognostic indicator. [32] Instead the location of the lesion affects the outcome with those arising on the arm doing better than those on the leg, which do better than those on the head and neck with finally those lesions on the trunk have the worse prognosis. [46] This wide range of presentations can make both screening and diagnosis difficult. [23,34]

In 1970 Breslow noted that staging based on tumor thickness was the best prognostic indicator for survival of melanoma and this is still true today. [26] The deeper or thicker the lesion with spread into the dermis and subcutaneous layers of the skin the more advanced the stage of disease. [47] Before staging a melanoma lesion it must be classified into the tumor node metastasis (TNM) classification system developed by the American Joint Committee on Cancer (AJCC). [48] See Table 2.1. Important indicators for TNM classification and thus survival include lesion thickness, mitosis, ulceration, lymph nodes involvement with micrometastasis or macrometastasis, number of lymph nodes involved and if metastasis is present, the site of metastasis and lactate dehydrogenase (LDH) level. [17,18,47] The TNM classification underwent an important revision in 2009 with the removal of the Clark level of invasion and adding the mitotic rate. [18] The mitotic rate, or the proliferation of the melanoma lesion defined by number of mitosis/mm2, was identified as a powerful independent predictor of survival. Mitotic rate is second only to Breslow tumor thickness as a predictor for survival in localized melanoma. [17,18]

Table 2.1
TNM Classification for Melanoma [48]

T classification	Lesion thickness (mm)	Ulceration Status/Mitosis
TX	Primary tumor cannot be assessed	NA
T0	No evidence of primary tumor	NA
Tis	Melanoma in situ	NA
T1	<1.0	a. Without ulceration and mitosis < 1mm^2 b. With ulceration and mitosis < 1 mm^2
T2	1.01-2.0	a. Without ulceration b. With ulceration
T3	2.01-4.0	a. Without ulceration b. With ulceration
T4	>4.0	a. Without ulceration b. With ulceration
N classification	**Number of lymph nodes (LN)**	**Nodal Metastatic Mass**
NX	Regional LN cannot be assessed	NA
N0	0	NA
N1	1	a. Micrometastasis* b. Macrometastasis**
N2	2-3	a. Micrometastasis* b. Macrometastasis** c. In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M classification	**Site**	**Serum LDH**
M0	No detectable evidence	NA
M1a	Distant skin, subcutaneous, distant LN	Normal
M1b	Lung	Normal
M1c	All other visceral sites Any distant metastasis	Normal Elevated

NA: not applicable; LDH: lactate dehydrogenase
*Micrometastases are diagnosed after sentinel lymph node biopsy
**Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically

Following this classification a melanoma lesion is further sorted into stage I through IV by the AJCC cancer-staging manual. [48] Refer to Table 2.2. For research purposes the stages are commonly divided into early and late-stages with early-stage including localized disease, which is defined as stage, I or II. Late-stage includes regional disease defined as stage III and metastatic disease defined as stage IV. [21,47,49] Less than 5% of patients are diagnosed with metastatic disease while approximately 10% present with regional disease and an estimated 85% present with localized disease. [47] This meticulous staging process allows for an accurate diagnosis, treatment plan and prognosis.

Table 2.2
Melanoma Staging [48]

Stage	Tumor	Node	Metastasis
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T (1-4) a	N1a	M0
	T (1-4) a	N2a	M0
Stage IIIB	T (1-4) b	N1a	M0
	T (1-4) b	N2a	M0
	T (1-4) a	N1b	M0
	T (1-4) a	N2b	M0
	T (1-4) a	N2c	M0
Stage IIIC	T (1-4) b	N1b	M0
	T (1-4) b	N2b	M0
	T (1-4) b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Current recommendations for treatment are based on the stage of melanoma and the ability to completely remove the lesion surgically with clear margins. For all stages of melanoma wide local surgical excision is the primary treatment.[43,47] Although an excisional biopsy is preferred for pathology evaluation often an incisional biopsy, superficial shave biopsy, deep scallop shave biopsy or punch biopsy is performed. [43,50] The goal of the biopsy is to pathologically confirm the melanoma diagnosis; whereas the goal of the wide local excision with a margin of clear tissue is to achieve long-term control of the disease and potentially a cure. [51] The type of biopsy technique used does not influence patient outcome. [52] What is essential is the removal of the lesion via wide local excision with clear margins. Inadequate margins can result in local recurrence, metastasis and negatively impact survival. [53-55] The NCCN provides specific guidelines for the amount of tissue around a lesion that needs to be excised depending on the size of the lesion, referred to as the clear surgical margin. [47] Refer to Table 2.3.

Table 2.3
Recommendations for Surgical Margins [47]

Tumor Thickness	Recommended Clinical Margins
In Situ	0.5-1.0 cm
<1.0 mm	1.0 cm
1.01-2.0 mm	1-2 cm
2.01-4.0 mm	2.0 cm
> 4.0 mm	2.0 cm

Following the wide local excision a sentinel lymph node biopsy may then be recommended depending on the stage of disease. The AJCC melanoma staging committee recommendation states "that sentinel lymph node biopsy be performed as a staging procedure in patients for whom the information will be useful in planning subsequent treatments and follow-up regimens. Specifically, the procedure should be discussed with (and recommended for) otherwise healthy patients who have T2, T3 and T4 melanomas and clinically uninvolved regional lymph nodes; the procedure should be recommended selectively for patients with T1b melanomas". [18] If a positive lymph node is found then complete lymph node dissection should be completed and all additional areas of metastasis should be surgically removed. [47] These recommendations are based on the most current research in an area of great controversy, as it is still unclear whether a complete lymph node dissection increases overall survival. [28,56]

The effectiveness of non-surgical treatment is limited so it should not be considered unless surgical excision is not feasible. [57] If surgical removal of the lesion with clear margins cannot be obtained due the location of the primary lesion or if there is metastatic disease, then systemic treatment is warranted. [47] Based on the NCCN guidelines for stage III and IV disease, additional treatment following surgery is recommended including observation, systemic therapy with interferon or clinical trial with a new therapy. [47]

Systemic therapy options can include radiation therapy, chemotherapy and/or immunotherapy. Previously the melanoma treatment options were

sparse but in the last five years there have been considerable improvements with the addition of molecular targeted therapy. [41] In 2011 the Federal Drug Administration (FDA) approved systemic therapy with ipilimumab the only monoclonal antibody directed at cytotoxic T-lymph antigen. [47] As approximately half of patients with metastatic melanoma are BRAF positive the FDA approved BRAF kinase inhibitors; vemurafenib in 2011 followed by dabrafenib and trametinib in 2014. These drugs were all approved based on months of improved overall and progression-free survival, but come with high-grade, adverse effects and thus are reserved for treatment of recurrent disease. [47] Despite these advances, chemotherapy and systemic therapy provide only modest response rates affirming that early-stage diagnosis with wide surgical excision remains the key to melanoma survival. [47,57,58]

Incidence, Prevalence and Mortality rates

The incidence of melanoma in the US is increasing faster than any other preventable cancer. Between 2002 and 2012 incidence has increased by 1.4% annually with the average lifetime risk of developing melanoma at 2.1% in the US population. [7] In 2013 the overall age adjusted melanoma incidence rate was 21.8 per 100,000 and this is expected to only increase as no primary prevention has been implemented and from 1982 to 2010 incidence rates doubled. [3,7] The increase in incidence is at least partially attributed to the increase in early-stage detection and UVR exposure through recreational activities. [59] Yet, the sharpest increase in incidence has been seen in low SES communities, where individuals are less likely to be screened, indicating that the increase may not be simply an

artifact of screening. [2] In all population groups over the past few decades the proportion of thin melanomas diagnosed has increased while thick melanomas have decreased. This may be influencing the overall reduced mortality rates. [60,61]

The prevalence of melanoma is also increasing due to the over 75,000 new cases per year and only a 10% mortality rate. In 2005 there were 723,416 people living with melanoma and in 2013 this number had risen to 1,034,460. [7] Non-Hispanic white men and women in the US carry over 95% of the burden of disease. [62] While the incidence rate from 1982 to 2013 has risen steadily, the mortality rate has remained stable at around 10%. [3,7,42] The overall survival rate in the US has increased over the last twenty years from approximately 82% to 91%. [7] Generally, the 5-year survival of melanoma is over 90% with localized disease, but if the cancer spreads into the regional lymph nodes the 5-year survival is less than 50%, and with metastatic disease it is less than 10%. [45,47] Survival is dependent in part on the stage and subtype of melanoma followed by the treatment provided. [27,45]

Looking more specifically at stages, based on the AJCC staging database through 2008, the 10-year survival for a stage IA lesion is 93% but only 39% for a stage IIC lesion. [18] Additionally, a study by Ward-Peterson et al examined 185,219 melanoma cases from 1982 to 2011 and confirmed that the stage of diagnosis had a significant impact on hazard ratio. [63] They found that localized disease had a hazard ratio of 5.8 while regional disease had a hazard ratio of 31.5 and metastatic disease had a hazard ratio of 169.5. [63] Beyond disease stage it is known that for localized disease survival is impacted by tumor

thickness, ulceration, mitotic rate, site, gender and age. [54] Survival is also negatively impacted by lymph node involvement with 5-year survival for stage IIIA, IIIB and IIIC at 78%, 59% and 40% respectively. [18] Meanwhile, the one-year survival of a stage IV melanoma is a dismal 62% for an M1a lesion, 53% for a M1b lesion and 33% for a M1c lesion. In stage IV disease, an elevated serum LDH level at time of diagnosis is a negative prognostic indicator with a 32% 1-year survival rate compared to 65% in a patient with a normal serum LDH. [18]

Decades of research have established that melanoma incidence and in turn prevalence rates and often mortality rates, are also influenced by numerous factors at the individual and social level. These include age, gender, race, ultraviolet radiation (UVR) exposure, SES, marital status, geographic location, tumor histology, tumor location, insurance status, access to health care, and prevention efforts of sun-protective behaviors, risk awareness and early detection efforts. [6,7, 14-25,64,65] The individual factors of age, gender, race and disease subtype will be outlined here and then followed by social determinants. Later in this chapter additional risk factors and prevention efforts will be discussed in detail.

Age

Age is an important variable in both incidence and mortality rates. Melanoma is predominantly found in non-Hispanic whites with the highest incidence in males and those adults over 75 years old. [1,19,47,66,67] Over the past few decades, incidence rates began to level off in those less than 65 while it increased in those over 65. From 1983 to 2007, a 2-fold increase in incidence

was seen in men aged 60 to 64, whereas in men aged 75 to 79 there was a 4-fold increase. [68] This increase is mostly attributed to the growth in the geriatric population. [25] Among the elderly, it has been found that minorities, those who are single or widowed, have more comorbidities, reside in rural areas and communities with less education and more poverty are especially at risk for late-stage disease. [69]

Meanwhile, in young women where there has been an 800% increase in incidence from 1970 to 2009 that is attributed to risky health behaviors like tanning. [6,70] Early-stage melanoma is seen more commonly in women less than 40 years old and more commonly in men after age 40. [16] Older people do have poorer survival rates as those older than 70 tend to present with lesions that are thicker, more ulcerated and have higher mitotic rates. [71] This increase in mortality is also attributed to higher cumulative UVR exposure, later stage at diagnosis and poor access to medical care. Meanwhile, the decrease in melanoma deaths in those less than 65 years old is credited to early detection and improved treatment. [62]

Balch et al noted that age is an independent prognostic variable in melanoma and may represent a decline in host mechanisms associated with advancing age. [17] Comorbidities are often linked with age, as with increasing age comes increasing health concerns. Studies have linked Parkinson's disease, immunosuppression from organ transplant and HIV infections to an increased risk of melanoma. [72] Additionally, the variation in anatomic distribution of melanoma is age-dependent. Older people more commonly develop head and

neck melanomas with chronic sun exposure and have few nevi, whereas younger people develop truncal melanomas dependent on sun exposure early in life and have many nevi. [73]

Gender

It is estimated that in 2016 approximately 46,870 men and 29,510 women in the US will be diagnosed with melanoma. [74] In the US, melanoma is the fifth most common cancer in men and the seventh most common cancer in women.[74] Overall melanoma is more common in men with poorer survival rates than women for all stages and in all age groups. [74,75] In 2016 it is estimated that 10,130 people will die of melanoma with 66% of these deaths occurring in males.[74] Interestingly, in the US the overall melanoma incidence ratio by gender is age-dependent. For example, in women less than 49 years old, 1 in 206 will develop a melanoma lesion and only 1 in 297 men will. Contrast this to women older than 70 years old where 1 in 52 will develop a melanoma lesion while 1 in 33 men will.[74]

These statistics assist in explaining the finding that more than 50% of melanoma deaths are in white men older than age fifty. [2] Also, males tend to develop melanoma lesions on the head or neck while females develop lesions on the extremities or torso. [25] Younger age, female gender and specific anatomic sites, such as the upper limbs, are related to better overall survival. [45] A higher rate in men is attributed in part to lower rates of sun protection behaviors, less use of sunscreen and more time spent outdoors per lifetime compared to women.[3] It has also been discovered that men are less likely to seek skin

cancer screening, report a concerning lesion or be concerned about previous sun exposure. [4]

Race

Those at highest risk for melanoma have light skin pigmentation and blonde or red hair. [23] Thus, Caucasians account for over 90% of melanoma cases reported in the US. [76] The incidence of melanoma both early and late-stage is highest among non-Hispanic whites even when adjusting for SES. [16] Yet, Hispanics, Asians and Blacks have higher percentages of late-stage disease. [6] Although there has not been a change in the overall mortality rate over the past decades, there is inequity in the demographics of melanoma mortality. [6,45] For example, the overall 5-year survival of melanoma from 2005 to 2011 was 70% for blacks while it is 93% for whites. [65] This difference in survival is impacted mostly by the later stage of diagnosis seen in minorities. A study of 1,690 melanoma cases in Florida demonstrated that late-stage disease was more common in non-Hispanic blacks and Hispanics at 52% and 26% compared to whites at 16%. [64] Yet, even when diagnosed with localized disease a disparity in survival is present with 5-year survival at 86% for blacks and 97% for whites. [77] This difference in stage of diagnosis and survival in minorities is attributed in part to the location of the lesions (the majority of lesions are on non-exposed skin areas), decreased suspicion by clinicians and patients and limited access to health education resources or health care. [3,25]

Subtype

Although not as predictive as stage, the subtype of melanoma at diagnosis contributes to the prognosis. Superficial spreading and lentigo maligna are both favorable subtypes with 95% 5-year survival rate. [45] Meanwhile, acral lentiginous has a poor prognosis with 5-year survival as low as 83% and is seen more commonly in minority populations. [6,45] The most dangerous subtype is nodular melanoma, comprising only 10% of all cases but is greater than 50% of all deep (> 2 mm) lesions. Nodular lesions grow quickly and develop as new lesions that are difficult to screen for because they do not following the typical asymmetry, border irregularity, color, and diameter (ABCD) criteria. [78,79]

Social Determinants

While the complex interplay of genetics and UVR exposure leads to the development of melanoma it is apparent that the incidence rate is influenced also by social factors. The effect of SES on melanoma incidence, disease stage and survival is well documented in the literature but this interaction is multifaceted and often difficult to measure. [6,80] Thus, contextual variables that have been used as surrogates for SES including education level, unemployment rates, poverty level, occupation type and median household income. [6] A contextual variable summarizes the characteristics of the individuals in the group. [81] Therefore, the contextual variable does not characterize the individual but the group as a whole.[82] This may deliver insight into the individual that is not otherwise available and even more importantly offers community level information to individual health outcomes. [83]

The best example of how individual and social factors are intertwined is UVR exposure and SES. Increased UVR exposure through outdoor recreation and leisure is a product of SES itself. It is hypothesized that affluence increases geographic mobility as well as leisure time that is then linked to UVR exposure. [16] This exposure to the sun is the only modifiable risk factor for melanoma development. [23] UVR exposure is often a personal decision but impacted by SES via education, occupation and geographic mobility. [6] It is unclear if SES affects melanoma independently or if SES is a proxy for UVR exposure. [84] Regardless of this relationship, it is known that SES continues to influence the incidence of melanoma even when controlling for age, gender, UVR exposure and race. [6] For example, an analysis of California data from 1988 to 2007 showed that Hispanics of lower SES had higher risk of thick tumors and nodular melanoma than Hispanics of higher SES indicating that SES impacts minorities as well. [2]

A review of over forty research articles on the influence of SES on melanoma by Reyes-Ortiz, Goodwin and Freeman explained that the positive social gradient of melanoma is a confounder of genetics, UVR exposure and increased screening. [6] Those cases of melanoma with high SES also tend to have a genetic predisposition to skin cancer through fair skin, light hair and propensity to get sun burns. [6] This is true in the US where over 90% of melanoma cases occur in Caucasians. [76] Winter vacations to warm locations and leisurely summers in the sun provide opportunities for increased UVR exposure among people with high SES. [6,61] Also, those with affluence and

access to health care are more likely to be screened for melanoma leading to earlier and more frequent detection. [6]

Education historically has been the most commonly used contextual variable for SES because it is easy to measure, commonly reported and stable throughout a lifetime. [83] To clarify the effect of education level on melanoma diagnoses Pollitt et al surveyed 566 newly diagnosed patients. [20] Those surveyed with lower education levels were more likely to report a belief that melanoma was not very serious and never thinking of themselves as being at risk. Lower education was also strongly associated with less knowledge about melanoma detection. Patients at all education levels appeared to have relatively equal access to health care but those without a college education were significantly less likely to have received a clinical skin examination. People without a college education were less likely to have talked with a physician about melanoma, been told they were at risk of skin cancer, instructed to keep an eye on a certain mole or instructed on how to look at their skin for signs of melanoma. Patients without a college education were also 3.4 times more likely than college educated patients to report competing health concerns with their melanoma diagnosis. [20]

Unemployment has also been used as a contextual variable for SES and appears to have a positive effect on melanoma rates. Counties with low unemployment were found by Singh et al to have the highest rate of melanoma when compared to high unemployment counties, incident ratio (IR) 30.1 and 23.1 respectively. [16] However, studies have found unemployment to be less important than the type of occupation. There is a paradoxical relationship in which work-

related UVR appears to lower the risk of melanoma in outdoor workers compared to indoor workers. This may be because continual frequent exposure of sun poses less risk for development of melanoma than the episodic infrequent, intense exposures that may cause sunburns. [61] For example, a few studies have noted an increase in melanoma in airline crews related to their increased opportunity for recreational sun exposure. [86,87]

It has also been noted that geographic location effects melanoma incidence and this is thought to be due to the social aspects of topography. A geographic location often embodies health care access, demographic factors of the population and UVR exposure. [15,16,85] For instance, when comparing metropolitan and rural areas in North Carolina it was noted that rural patients were older and more likely to live in poverty. [85] When Singh et al compared melanoma incidence between rural, urban and metropolitan areas, they found the highest incidence for all melanoma cases in metropolitan areas (IR 30.5), followed by urban (IR 25.4) with the lowest rate in rural areas (IR 23.2, $p < 0.05$).[16] This trend was noted also for early-stage disease, but for late-stage disease metropolitan and rural incidence rates were equivalent. Yet, upon multivariable analysis, county population was not significant for melanoma incidence. [16] Higher age specific rates of melanoma are also seen in areas of the US with higher UVR exposure. [15] Alaska, for example, had the lowest rate of melanoma from 2002 to 2006 with 13/100,000 cases compared to Hawaii with 62/100,000 cases. [67] Additionally, as expected, an analysis of UVR exposure in

the US found that both early and late-stage melanoma incidence rates were significantly higher in counties with high UVR levels compared to low levels. [15]

Risk Factors, Prevention and Screening

Development of a melanoma lesion involves a complex and not well-understood interaction between individual and social factors. Individual factors include the nonmodifiable risk factors of age, gender, race, genetics, family history of melanoma, personal history of melanoma, lighter skin pigmentation, blond or red hair, blue or green eyes, increased number of nevi and a tendency to get sun burns. Of these risk factors, hair color and pigmented nevi are the strongest and most consistent predictors of risk. [23] Significant study has been given to modifiable risk factors including smoking, diet, hair dyes, fluorescent lighting, hormone therapy and stress, but no association with melanoma has been found. [61,80] A meta-analysis by Jiang et al shows some studies with an association between obesity and melanoma incidence and mortality and some without. [80] Likely though, body mass index is playing a role in screening where those with an increased body mass index have decreased screening behaviors. [80] To date, the single modifiable risk factor is sun or UVR exposure. [23] Intense and intermittent sun exposure with sun burns especially before the age of fifteen is a strong predisposing risk factor for melanoma later in life. [23] UVR exposure via natural sunlight or artificial tanning is correlated with SES, as affluence affects leisure time and the ability to travel to areas with higher UVR radiation. [84]

Despite significant research there is incomplete evidence regarding the nature, timing and extent of UVR exposure and its relationship to melanoma

development. [15,23] It is acknowledged that there is a difference in melanoma subtype based upon chronic sun exposure and non-chronic sun exposure but this will remain a difficult area of research due to the limited ability to measure sun exposure in a retrospective study and the lack of cohort studies due to the rarity of melanoma cancers. [37,88] Various aspects of sun exposure have been studied including smaller swimsuits, population migration to the equator, thinning of the ozone layer and increased tanning bed use. [61,89] UVA and UVB exposure are known to cause melanoma with UVB exposure coming from sun exposure and tanning bed use. [23,61] It is known that sunburns at a young age are a risk as is cumulative sun exposure. [25] A meta-analysis of over fifty articles on sun exposure and melanoma risk noted that intermittent sun exposure and sunburns are risk factors but surprisingly high occupational sun exposure is not. [88]

A common form of intermittent sun exposure is tanning beds as approximately 30 million people use tanning beds each year. [89] An analysis of US tanning bed use found that approximately 35% of adults, 55% of university students and 19% of adolescents have used a tanning bed. Regardless of age, it is known that women tan more often than men. [90] Despite the tanning bed industry insistence that tanning beds are safe, substantial evidence has indicated an association between tanning bed use and melanoma. [23,89,91-93] The 7 to 20 year lag between UVR exposure and development of a melanoma lesion further complicates analysis. [89,91] Despite this long time period, numerous studies have found that a modest, yet significant increase in risk from tanning bed use. [94] The tanning bed industry states that tanning beds emit more UVA radiation than UVB

but the National Toxicology Program states that both UVA and UVB are reasonably anticipated to be human carcinogens. [95] A study by Ting et al found that women less than 45 years old with a history of tanning bed use had a three-fold increased odds of melanoma compared to those women who reported never using a tanning bed. [92] The population attributable risk of tanning bed use is 2.6% to 9.4% of melanoma cases. [96]

Primary and secondary prevention of melanoma through sun-protective behaviors, risk awareness and early detection efforts are crucial. Sun-protective behaviors include avoiding sun exposure and tanning beds, wearing protective clothing and liberal use of sun screen. [23,25] The protective effect of sunscreen is only circumstantial, but practical evidence would suggests that since UVR is a risk factor for melanoma and sunscreen decreases UVR absorption then melanoma would be prevented. [97,98] Teaching these protective behaviors to children is fundamental as the risk for sunburns is most acute during early childhood. Additionally, behavioral patterns and attitudes toward sun exposure develop early on, determining both adolescent and adult behaviors. [23] To protect children, the World Health Organization and the International Commission on Non-Ionizing Radiation Protection recommend against those less than eighteen years old from using artificial tanning devices. [99,100] In the US, California and Vermont have been the first states to ban the use of tanning beds by people less than eighteen years old. [101]

The need for public and health care provider education regarding the risk and recognition of melanoma lesion was acknowledged in 1985 with the

development of the asymmetry, border irregularity, color and diameter (ABCD) criteria. [24] The ABCD criterion describes a suspicious lesion as one that is asymmetric, with irregular borders, has multiple colors and with a diameter greater than 6mm. This acronym was developed to be a simple tool for both the general population and medical community to recognize thin melanoma lesions. The ABCD criterion has been shown to be both sensitive and specific for melanoma. After decades of use the ABCD criteria has expanded to the ABCDE criteria with the addition of the term, evolving. Evolving recognizes the change in shape, size or symptoms of a lesion, which is especially important for nodular melanomas. [24] This effort to increase awareness of the risk of melanoma has increased screening rates and the detection of earlier stage lesions. [59,62,101] Research has shown that even a one-time instruction regarding the ABCDE criteria can improve recognition of a melanoma lesion both in the general population and by clinicians. [102,103] Meanwhile, an increased awareness of melanoma was associated with both a decreased time to seek medical attention for a suspicious lesion and thinner lesions. [104] Education of the public is important because patients find the majority of melanoma lesions themselves although if found by a clinician the lesion tends to be thinner. [25,105]

To date, there has been no community-based randomized trial conducted to demonstrate the decrease in mortality from screening asymptomatic persons for melanoma. This lack of evidence is due to the low rate of melanoma mortality and high costs associated with such a study. Thus, no recommendation for routine population-based screening can be made and the US Preventative

Services Task Force reports that there is insufficient evidence to recommend regular skin checks on the general population. [4,5] Additionally, there are no recommendations published for eye exams, oral exams or pelvic exams to monitor for mucosa melanoma lesions. [44] Following melanoma treatment there is also a lack of clarity on recommended long-term follow up. It is estimated that there is an increased risk of developing a second primary melanoma of 8-10%, yet intensive long-term follow up beyond five years is likely not cost effective. [106-108]

Despite the lack of evidence, the American Cancer Society recommends that all people between the ages of twenty and forty be screened via clinical skin assessment for melanoma. [1] At the same time, the American Academy of Dermatology has developed a personal screening program, Body Mole Map, recommending that patients perform skin self-assessments and record changes. However, they do not specify the frequency of self-assessments, nor do they specify how often clinician provided exams should be completed. [109] With the community and clinicians receiving these mixed messages regarding screening, it is not surprising that participation in screening is limited.

It is known that approximately 10% to 25% of the US population practice regular skin self-examinations. [110] It is estimated that a skin assessment by a dermatologist is 89% to 97% sensitive for melanoma diagnosis. [23] Yet, only 8% to 21% of the population receives annual clinical skin exams. [111-113] A study by Swetter et al noted that thinner lesions were found in people who the year before had regularly examined their own skin, consulted a physician at least once and

received a full body skin exam by a clinician. [105] But, interestingly in this study the benefit of the full skin exam by a clinician was limited only to men over sixty; in this age group there was a 4 times greater odds of a thin tumor compared to men who did not receive a full skin exam by a clinician. [105] Meanwhile, it is known that females and those with continuous Medicaid insurance are more likely to seek screening and care for a concerning lesion, while at the same time race, SES, health insurance status and access to health care all further influence screening behaviors. [6,20,66,114] For example, in the Appalachian area of Kentucky access to health care, limited finances and low education levels are all known barriers to getting cancer screenings. [115]

Additionally, the health care system itself also influences melanoma screenings. Many experts argue that primary care physicians are critical to melanoma control but others question if they have appropriate training or enough time to conduct adequate skin exams. While only 13% of the population reports having a dermatologist, 85% report seeing a physician within the last two years.[116] As the majority of health insurances require a referral to see a dermatologist, this reinforces the role of the primary care provider in evaluating suspicious lesions. [4] A meta-analysis noted that from 1987 to 2004 the number of primary care physicians who performed full-body skin exams actually decreased.[117] Time constraints, competing comorbidities and patient embarrassment were listed as barriers to completing full skin exams in a survey of 1600 physicians. [104] An analysis of the National Ambulatory Medical Care Surveys from 2005 to 2010 found that a patient was more likely to receive a skin

examination at a primary care office if they saw a physician assistant or nurse practitioner. [118] With such inconsistency in screening guidelines and practice it is apparent that subsets of the population could be at risk for later stage diagnosis.

Disease Stage

The stage at which melanoma is diagnosed directly impacts prognosis and survival. [27] Melanoma is staged by the AJCC cancer-staging manual and classified into stages I through IV. These stages are frequently categorized into early and late-stage with early-stage including stages I and II while late-stage includes both regional disease, stage III, and metastatic disease, stage IV. [21,47,49] SEER data from 2009 indicated that the 5-year survival for localized, regional and metastatic melanoma is 98%, 62% and 15% respectively. [21] Over the past few decades there has been an increase in proportion of thin lesions diagnosed with a corresponding decrease in thick lesions, which is likely impacting the decreasing mortality rate. [60,61]

Social factors that have been shown to influence the stage in which a lesion is diagnosed include SES, geographic location, employment or occupation, marital status, health insurance status, physician population ratio and access to health care. [6,14-16,20-22] The effect of SES on melanoma is two-sided with high SES linked to high incidence rates with early-stage disease and low SES linked to lower incidence rates but poorer outcomes. [6,16] The positive social gradient of melanoma disease stage is well supported in the literature via multilevel analyses, case-control studies and surveys. [2,6,14,16,20,66,84,119] Singh et al provided the most comprehensive review of SES with a multilevel Poisson

regression of 130,359 melanoma cases from the 2004 to 2006 SEER data which found higher county incidence ratios for all cases of melanoma where there is lower poverty, a higher education level, a higher median household income and lower unemployment. [16] Low poverty counties had a significantly higher IR of melanoma compared to high poverty counties (IR 27.6 vs 15.9, $p < 0.05$). [16] Also, the incident rate for all cases was 47% lower in counties with low education levels compared to those with higher education levels. For early-stage, late-stage and all cases of melanoma the incidence rates were highest in counties with a high median household income. [16]

Although melanoma is unique with a positive social gradient this cancer is similar to other cancers in that poverty level is associated with late-stage disease. A study by Greenlee et al evaluated 2 million cancers in the US from 1997 to 2000 and melanoma had a two times increased odds of late-stage disease when comparing the counties with the highest poverty to the lowest. [120] Hu et al who completed a spatial analysis of melanoma cases in Florida confirming this juxtaposition where for every 1% increase in population living in poverty they noted a 2% increase in late-stage melanoma cases. [121] A person's geographic location also has a social influence on disease stage with early-stage diagnosis more common in urban areas where the counties have higher education levels, higher incomes, less poverty and higher rates of health insurance. [15]

A study by Youl et al of 3,762 cases and 3,824 controls evaluated the impact of SES on melanoma lesion thickness by evaluating education,

employment status and marital status. [122] The multinomial regression model found the variables of not working, not married and lower education level to each be significantly associated with an increased risk of having a thick melanoma lesion. Additionally, not having a clinical skin examination within three years of diagnosis was associated with a 45% increased risk of a thicker lesion. (RRR 1.45, $p < 0.001$) [122] Education is known to influence position in society, access to health care, access to health information and therefore health decision making. Youl et al suggests that a clinical skin examination may be a mediator between education and lesion thickness. [122]

One factor that has been found to be protective for melanoma diagnosis and survival is marriage or living with someone. [122,123] Van Durme et al noted a 53% increased risk of late-stage diagnosis of melanoma in unmarried people. [124] A study on people over 65 years old by Reyes-Ortiz et al described that being single or widowed increased the risk of late-stage melanoma diagnosis and significantly lowered survival. [19] McLaughlin, Fisher and Paskett evaluated the effect of marital status on the stage of diagnosis of 192,014 melanoma cases from 1973 to 2004. [21] Among men, the odds of late-stage melanoma versus early-stage was 1.31 for widowed, 1.56 for those never married and 1.60 for those separated or divorced. For women the odds of late-stage versus early-stage melanoma was 1.93 for widowed, 1.25 for never married and 1.57 for divorced or separated. [21]

These findings highlight the relationship between gender and marital status revealing the protective effect of marriage for both sexes. These

differences are considered to be due to the social support, insurance status and prompting to access healthcare that is received from a spouse. The increase in access to health care noted in married people could also be due to the spouse spotting a lesion, peer pressure to seek screening or assistance from a spouse for daycare or transportation to seek a clinical evaluation. [21]

To have access to the US health care system the individual needs health insurance coverage and the community needs an adequate health care workforce. Having health insurance in the US allows one to afford screening and treatment. Research has shown that having health insurance increases screening rates, which in turn leads to an increase in measured incidence rates.[6,20,66] Analyses of those diagnosed with melanoma have shown that lack of insurance or insurance with Medicaid or Medicare increases the risk of late-stage diagnosis. [125] Meanwhile, a study of the primary care physician supply in Ohio found a decrease in late-stage melanoma cases associated with an increase in physician density but most significantly among those with insurance. [126]

Roetzheim et al reviewed the supply of dermatologists and family physicians in Florida and earlier detection of melanoma was associated with an increase in both types of provider. [22] They establish that for each additional dermatologist and family physician per 10,000 populations there was an increased odds of early diagnosis by 39% and 21% respectively. [22] Another study evaluated the distance a patient would have to travel to see a clinician in North Carolina and found that for every one-mile increase in distance there was a 0.6% increase in Breslow thickness; therefore, a ten-mile or longer drive to a

clinician was associated with a clinically significant increase in melanoma lesion thickness. Interestingly, there was a decrease in Breslow thickness for those patients who drove over 120 miles to seek care, which supported previous research showing a protective benefit for those patients who have the ability to travel long distance to seek superior health care. [85,127]

Of interest, those who resided in a county that had a dermatologist traveled on average 8.3 miles less than those who resided in a county without a dermatologist. This impact was seen even if the patient did not actually see the dermatologist suggesting that the presence of a dermatologist was actually a marker of an increase in supply of health care providers in general. [85] A positive effect on early-stage of melanoma diagnosis is seen for increased physician density and recent primary care physician visit. [15,116] Additionally, an increase in dermatologist density is associated with decreased melanoma mortality. [128] These studies confirm the social and geographic barriers that then affect melanoma disease stage.

Treatment

Surgery is the only potentially curative treatment for melanoma. Surgery for localized disease, stages I and II, includes wide local excision of the primary tumor and may include excision of lymph nodes. A biopsy followed by wide local excision is critical for diagnosis, staging and disease free survival. [129] As Breslow thickness increases overall survival decreases. A patient with a lesion less than 1mm has a greater than 85% 5-year survival, while a patient with a lesion thicker than 4mm has less than 50% 5-year survival rate. [85] For localized disease,

Breslow tumor thickness, ulceration and mitotic rate predict disease outcome. [58] The NCCN provides melanoma treatment guidelines that are supported by an abundance of clinical trials; they have determined that at least 1 cm and no more than 2 cm of clear surgical margins is adequate treatment. [47,51,130] Refer to Table 3.1. These recommendations are considered the standard of care treatment that should be provided to all patients unless not appropriate for a specific patient based on their medical situation. [47] It is known that inadequate margins result in higher rates of loco-regional metastasis but wide margins lead to increased morbidity and a poor cosmetic outcome. [51,53] Therefore the goal of surgical treatment is to optimize local control with potential cure while minimizing morbidity. [51]

The recommendation to provide a clear margin of 1-2 cm around a melanoma lesion is due to the propensity of melanoma to disseminate and recur locally. Local reoccurrence occurs in approximately 5% of cases but in lesions larger than 4mm can occur in up to 12% of cases. [131,132] Local recurrence does not occur only from inadequate surgical excisions but can be a manifestation of an aggressive, ulcerative and thick primary lesion. [54,131] On average local recurrence is seen in 10.5% of head and neck melanomas compared to only 3.8% in trunk and extremity lesions. [133] Local recurrence is usually associated with the development of systemic metastasis and a poor prognosis of less than a 5% chance of survival at 10 years. [131]

Several studies have confirmed that inadequate surgical margins are correlated with local recurrence. [51,53,54,58,134] It is known that in head and neck

lesions positive margins are seen in 6-21% of cases. Risk factors for positive margins include ulceration, increased tumor thickness, recurrent tumor and advanced age. [133] A study by Foster, Velasco and Hieken 2008 noted recurrence of disease in 36% of patients with inadequate margins compared to 12% of those with adequate margins. [134] However, these studies have not shown a significant correlation between surgical margins, recurrence of disease and survival.[51,53,54,58]

A Cochran review by Sladden et al of five randomized control trials of wide local excisions of primary cutaneous melanomas noted that none of the studies showed a statistically significant difference in overall survival when comparing narrow versus wide excisions. Of note, the study by Balch et al, which compared narrow margins of 2 cm to wide margins of 4 cm, was used in developing the most recent NCCN guidelines that established that a margin larger than 2 cm does not improve patient outcomes. [54] Even with excessively wide margins of 2-4 cm, Sladden et al explained that the point estimate for overall survival favored wide excision by a small degree (HR 1.04). [58] The inability to demonstrate the effect of clear margins on survival is attributed to the lack of size and power of the studies due to the low rate of local reoccurrence and even lower effect of clear margins on melanoma specific deaths. Additionally, when local reoccurrence does occur it does not cause metastasis that impacts survival. [51,55] As the effects of inadequate margins is still under investigation the current belief is that inadequate margins increases the risk of local reoccurrence and therefore may be associated with increased mortality. [53-55]

Despite the abundant effort to provide medical guidelines, research in the United States shows that generally medical guidelines are followed only 55% to 75% of the time. [135,136] Although these guidelines were not developed for strict adherence this low rate is surprising. More concerning is whether variation in adhering to these guidelines is also a sign of inequity in health outcomes. Studies have shown that this noncompliance with cancer treatment guidelines is present for other cancers as well. For example, adherence to recommended chemotherapy for breast, lung and colon cancers has been shown to occur more frequently in higher SES areas. [137-139] This may be due to availability of treatment because seventy percent of chemotherapy is provided in the outpatient setting.[140] Whereas for melanoma, Reyes-Ortiz noted that younger age; marriage and SES were independent predictors of receiving chemotherapy treatment. [141]

Looking at melanoma surgical treatment, Cormier et al provided an analysis of 1998 to 2001 SEER data on 18,499 cases of melanoma and found that 31% of stage 1A, 40% of stage IB and II and 69% of stage III cases were provided surgical treatment according to the NCCN guidelines. [28] An analysis by Wasif et al of 35,126 melanoma cases from SEER data from 2004 to 2006 found noncompliance with surgical margins in 68% of cases. Less than a 1 cm margin was resected in 62% of T1, 44% of T2, 41% of T3 and 42% of T4 cases. [142] Wasif et al then completed an analysis of 2004 to 2008 SEER data that showed that only 40% of the 60,194 cases underwent wide local excision with at least a 1 cm margin. [153] A community-based study of 252 clinically node negative melanoma cases found that 87% of Tis and T1 tumors followed NCCN treatment

guidelines while only 60% of T2-T4 tumors were compliant. [143] These studies demonstrate the lack of surgical treatment adherence in melanoma. If there were better adherence to melanoma treatment guidelines it would most likely improve morbidity and mortality.

While there is an abundance of research on the factors that influence melanoma incidence and mortality the research on surgical treatment adherence is anemic. Research on the variance in surgical treatment for melanoma includes stage of disease, anatomic site of lesion, age, race, poverty, marriage, geography, health care system and type of health care provider.[28,53,54,85,123,129,132,143-149]

The lower the stage of disease the more likely inadequate margins will be excised revealing a bias that localized disease is less concerning. [53] Meanwhile, numerous studies have noted that the anatomic site of a lesion, most commonly the head and neck, plays a significant role in lesions being left with inadequate margins. [145] This is understandable due to cosmetic concerns but this places the patient at risk as T3 and T4 lesions most commonly have positive margins and head and neck lesions have the poorest prognosis compared to other anatomical sites. [54,148]

The age of the patient is likely a corollary for comorbidity and has been consistently associated with noncompliance of treatment recommendations. [142] Numerous studies have found that the risk of a patient not being provided the recommended melanoma surgical treatment is associated with older age, especially greater than 80 years. [28,132,142,145] One study determined that

compared to those aged less than 35 years, patients' aged 65 to 74 had 1.37 odds of inadequate treatment while those over 75 years had 2.38 odds. [28] Another study discovered that the odds that a doctor would not comply with treatment guidelines increased 2.6% per life-year. [132]

The effect of age on treatment is understandable but inadequate surgical treatment of melanoma has also been associated with race. [142,146] The multivariate analysis by Wasif et al of the 2004 to 2008 SEER data revealed that the race of "other" had a three times greater odds of inadequate surgical margins compared to the white race group. Also, blacks had a 1.59 odds and the "other" race group had a 2.81 odds of noncompliance with sentinel lymph node biopsy (SLNB) recommendations compared to whites. [142] An analysis by Collins et al of melanoma surgical treatment from 1973 to 2004 on SEER data showed that blacks were less likely to receive any surgical treatment but more likely to undergo amputation. [146] This analysis of over 150,000 cases also revealed that melanoma specific and 10-year overall survival of blacks was poorer than for whites regardless of surgical treatment. [146]

The only study to date on SES and surgical treatment, Al-Qurayshi et al analyzed 2,765 discharge records from patients who underwent skin excisions and revealed that patients with low annual incomes were more likely to be treated in a non-teaching, rural or low volume hospital compared to high annual incomes. [144] At the same time, low-income patients and Medicaid patients were more likely to be treated by a low volume surgeon. [144]

While poverty appears to negatively affect treatment, marriage seems to have a protective effect, as those separated, divorced or widowed were less likely to receive surgical treatment per the NCCN guidelines. [28] Place of residence also impacts surgical treatment as a comparison of rural and urban counties noted that those in rural counties had a 13% decreased odds of receiving SLNB compared to those residing in urban counties. [147] A study by Martinez et al supports this finding noting that residents in the Southern United States are 46% less likely to receive a SLNB compared to the Western United States. [150] State specific variations were also dramatic with 36% of Connecticut cases and 76% of rural California cases with inadequate margins.[53] Meanwhile those residing in the state of New Mexico had an almost 4-fold increase in odds of non-adherence to surgical treatment guidelines compared to those in the city of San Francisco-Oakland. [28]

Meanwhile, various studies show that two other variables that could add to the discrepancy in melanoma treatment are the health system itself and the type of health care provider. [85,143,149] There are differences in the health care provided in small community hospitals and large medical centers. To this point, a study by Rivard et al hypothesized that the large referral cancer center would better adhere to the NCCN melanoma treatment guidelines. [149] They found instead a decreased adherence to the wide local excision guidelines but better adherence to the SLNB guidelines in the referral cancer center compared to outside the centers. The diminished adherence to the wide local excision guidelines was attributed to more complex cases referred to their center and outside research

indicating that less experienced cancer centers tend to take excessive surgical margins. Of interest, the cancer center itself did significant impact surgical treatment provided but the overall survival was not significantly different. [149]

Since melanoma treatment is provided by a wide variety of health care providers it makes sense that this would impact the treatment given. A study of melanoma treatment by Stitzenberg et al in North Carolina revealed that the health care provider and their practice patterns influenced the treatment offered, which may influence patient outcomes. [85] Particularly, they noted that surgeons affiliated with multidisciplinary melanoma programs were more likely to provide sentinel lymphadenectomy while those affiliated with academic centers were most likely to have access to clinical trials. [85] Another study evaluated the treatment provided at one community teaching hospital and despite easily accessible standards, physician education seminars and weekly multidisciplinary tumor board conferences there was a wide variation in melanoma treatment. [143] Specifically, compliance with the NCCN guidelines for surgical margins was dramatically different between non-surgical oncologist and surgical oncologist, with 95% and 38% respectively. [143] These studies demonstrate that a wide variety of intentional and unintentional factors may be influencing melanoma surgical treatment.

Conclusion

As the rate of melanoma continues to rise there is an urgent need to better understand the risk factors, individual and social that define the population most at risk. This literature review demonstrates that those diagnosed with late-stage

melanoma are likely a vulnerable sub-population. Additionally, this literature review highlights inequity in health care delivery that needs further clarification. This captstone hopes to add to the literature on the social determinants of health that may be impacting late-stage disease diagnosis and non-adherence to surgical treatment guidelines. The purpose of this capstone is to help guide further public health interventions for melanoma in Kentucky.

This concludes the comprehensive literature review of melanoma pathophysiology, staging, treatment, incidence, prevalence, mortality, risk factors, prevention, screening recommendations and discussion of the factors that have been shown to effect melanoma stage of diagnosis and adherence to surgical treatment guidelines. The following two chapters will encompass paper one which analyzes the factors influencing diagnosis of late-stage melanoma and paper two which analyzes the factors influencing non-adherence to melanoma surgical treatment guidelines for early-stage lesions.

Chapter III

Individual and Social Factors Associated with Late-Stage Melanoma Diagnosis in Kentucky

Introduction

Malignant melanoma is the most deadly form of skin cancer, yet it still has a good prognosis with a 90% survival rate. [32,45] This high survival rate is because 85% of melanoma lesions are diagnosed at an early-stage. The 5-year survival rate for localized, regional and metastatic melanoma is 98%, 62% and 17.9% respectively. [7] Over the last few decades the incidence of melanoma has steadily risen. The age-adjusted incidence rate of melanoma in the US is 21.8 cases per 100,000 population while the age-adjusted mortality rate is 2.7 per 100,000. [7] Meanwhile, in Kentucky the age-adjusted incidence rate of melanoma is 24.3 cases per 100,000 population while the age-adjusted mortality rate is 3.4 per 100,000. [7]

Unlike other forms of cancer, melanoma is most likely to occur in those with a higher socioeconomic status (SES) and generally is considered a disease of wealthy white individuals. [6] Despite this, it is known that people with lower SES, regardless of race, are more commonly diagnosed with an advanced disease stage. [6] Also, earlier detection of melanoma lesions has been associated with physician density of both family physicians and dermatologists. [22] Due to these disparities, it is important to determine how the characteristics differ between those diagnosed with early-stage and late-stage melanoma.

The best indicator for melanoma survival is the stage in which the lesion is diagnosed. [26] Melanoma is staged first by determining the size of the lesion, extent of lymph node involvement and if the tumor has metastasized. [47] Using this information, the American Joint Committee on Cancer (AJCC) staging manual then categorizes the lesion into stage I through IV. [48] Often these stages are further merged into early (stage I and II) and late (stage III and IV). [21] Refer to table 3.1. The stage at which a melanoma lesion is diagnosed then determines the treatment course and outcome of the disease. [47]

The factors that influence the stage in which a melanoma lesion is diagnosed have been an area of significant study. The literature elucidates the influence of individual variables such as risk awareness, ultraviolet radiation (UVR) exposure, age, gender, race, marital status, tumor histology, tumor location and health insurance status on melanoma disease stage. [15,17-19,21,23,25,74,125] Additionally, the influences of geographic region, SES and health care access have been established. [6,15,22] SES itself and the link between SES and individual health is difficult to measure, so surrogate measures are utilized.[6,83]

Education and poverty are often used as indicators of SES as education is usually a stable marker throughout life and poverty has been associated with several health outcomes. [83,152] Several studies have found an association with both low education levels and high poverty levels and late-stage melanoma lesions. [16,121,122,152]

In addition to SES, the inability to access the US health care system is associated with diagnoses of later stage melanoma. [125,126] Accessing the US health care system is complex with the anemic physician workforce at the center of the crisis. In 2015 the American Academy of Medical Colleges (AAMC) reported that the demand for physicians continues to grow faster than the supply leading to a projected deficit of up to 90,400 physicians by 2025. [153] The shortage of dermatologist is expected to only continue, especially in rural areas, as the incidence of skin cancer increases and the capacity for training programs stagnates. [154]

Kentucky is an exceptional population to study the effect of SES and physician density on melanoma disease stage. With a majority white population, Kentucky has an above average rate of melanoma and a high mortality rate. [155] At the same time, Kentucky has higher rate of poverty and wider variance in the percentage of the population by county without a high school education compared to other US states. [156] Furthermore, this rural state ranks in the bottom one-third of states for active primary care physicians per 100,000 population. [157]

The purpose of this paper is to assess for any associations between individual and social variables and late-stage melanoma in white non-Hispanic Kentuckians from 1995 to 2013. We hypothesize that late-stage diagnosis is associated with an increase in poverty level, decrease in education level and decrease in physician density. This study intends to lend insight into the high mortality rate in the state by identifying characteristics of those diagnosed with late-stage disease.

Methods

Study population and data resources

Data on individual level variables were obtained from the Kentucky Cancer Registry (KCR) while community level variables were attained from the United States Census Bureau and the Kentucky Department for Public Health. The KCR is a statewide, population-based registry funded by the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program and the Centers for Disease Control and Prevention's National Program of Cancer Registries. [158] The KCR has 99% case ascertainment and has received gold certification from the North America Association of Central Cancer Registries each year since formal certification was established. [159]

All reported melanoma cases from non-Hispanic whites, 18 years or older from 1995 to 2013 were collected. Only non-Hispanic whites are described in this study due to the limited number of cases in other race groups. Cases that were in situ lesions or non-primary tumors were excluded. This provided data on 10,109 cases including individual data on age, gender, marital status, year of diagnosis, anatomic site of lesion, health insurance status, rural/urban, Appalachian/non-Appalachian and stage at diagnosis.

The 2000 United States Census Bureau provided county level data on percentage with high school education and percentage below the poverty level.[8,11] The Kentucky Department of Public Health provided 2006 physician licensure data with number of all-physicians, family practice physicians and dermatologists, in each county. [12] To determine the physician density the number

of all-physicians, family physicians and dermatologists, per 10,000 population by county was then calculated with the 2006 US Census Bureau intercensal population estimates. [159]

Outcome and Independent Variables

The outcome variable of interest is disease stage: early versus late. Stage at diagnosis was categorized into early and late-stage with early-stage as referent and defined as stage I and II lesions while late-stage was defined as stage III and IV lesions.

The independent variables of main interest are poverty level, education level and physician density. The percentage of the county below the poverty level and percentage with a high school education are provided as continuous variables. Physician density is evaluated with the continuous variables of all-physicians, family practice physicians and dermatologists. Total physicians was applied as melanoma is diagnosed by many types of physicians not only family practice physicians and dermatologists.

The year of diagnosis was categorized into five groups with 2013 to 2010, 2009 to 2007, 2006 to 2003, 2002 to 1999 and 1998 to 1995. Gender is categorical with male and female. Age was categorized into three groups with 65 and older, 64 to 35 and 34 to 18 years. Marital status is also categorical with married/partner, single, widow, separate/divorced and unknown. Health insurance status was categorized where primary payor types were grouped, with private insurance, uninsured, Medicaid, Medicare and unknown. Geographic

region includes two measures, urban/rural and Non-Appalachian/Appalachian. Urban is defined as Beale codes 1 through 3 while rural is defined by Beale codes 4 through 9. Non-Appalachian is defined by counties defined as non-Appalachian. [160] Anatomic site of the lesion is categorical based upon the area of the body.

Statistical Analysis

Descriptive statistics were used to describe the study population and the distribution of variables for all cases, early-stage and late-stage. A graph displaying the trend in melanoma incidence from 1995 to 2013 for early and late-stage disease by year of diagnosis was made. The proportion of the study population that died was calculated by early and late-stage disease and by gender.

Logistic regression was used to evaluate the unadjusted associations between each covariate and early-stage and late-stage disease groups. Covariates include age at diagnosis, gender, marital status, year diagnosed, anatomical site of lesion, health insurance status, urban/rural, non-Appalachian/Appalachian, poverty level, education level, and physician population ratio for total physicians, family practice physicians and dermatologists. The resultant estimated odds ratios (OR) and 95% confidence interval were reported. All significant variables were assessed for interaction effect and significant interaction terms were described and utilized in the final model analysis.

Multiple logistic regression was then used to formulate the final model of those with late-stage disease. The model was first run with all covariates and then variables were removed using backward elimination to find the model of best fit. All reported P-values are two-tailed with statistical significance set at an alpha level of 0.05. All analyses were conducted using SPSS version 23. [161]

Results

The demographic characteristics of the study population: all cases, early-stage and late-stage disease are described in table 3.1. There are 10,109 cases reported with 13.6% late-stage. Comparing early and late-stage disease groups, both have similar distribution of age with the mean age of all cases at 56.9 years with a standard deviation of 16.2 and a range of 18-102 years. The majority of cases occur in males with 63% of late cases found in males. Almost half of all cases, early and late-stage occur in married individuals.

The majority of all cases and early-stage cases are on the trunk and shoulders, hips, or limbs. Whereas almost a quarter of late-stage cases are defined as overlapping or not otherwise specified (NOS). Almost half of all cases, early and late-stage are reported in those with private health insurance. Late-stage cases are more commonly uninsured or insured with Medicaid or Medicare compared to early-stage lesions. Those who reside in urban areas and non-Appalachian counties report the majority of all cases, early and late-stage. The mean percentage of those living below the poverty level by county is 15.5% with a range of 4.1- 45.0%. The mean percentage of those with a high school education level by county is 74.5%, with a range of 49 - 87%.

The entire state of Kentucky has 9,109 physicians with a range of 0 - 56.5 per 10,000 population in each county. There are 1,361 family practice physicians with a range of 0 - 7.7 per 10,000 population in each county and 121 dermatologists with a range of 0 - 0.93 per 10,000 population in each county with the majority of counties without a dermatologist. There is a mean 20.9 all-physicians per 10,000 population for late-stage cases, compared to the early cases at 21.7. The number of family physicians and dermatologists was similar for early and late-stage groups.

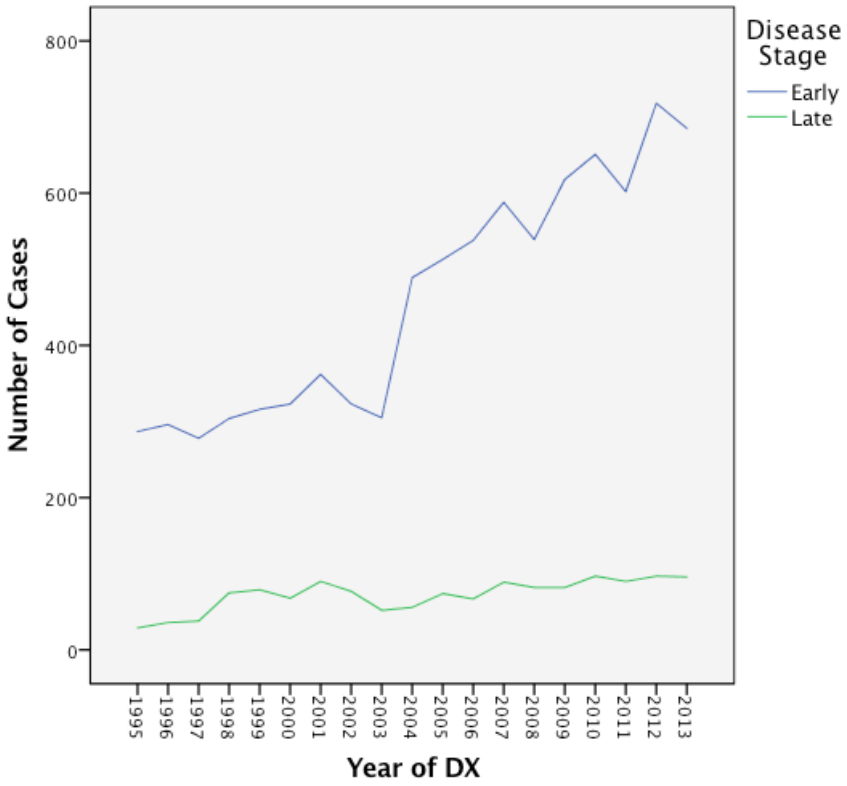
Table 3.1: Characteristics of Melanoma Cases by Disease Stage in Kentucky from 1995-2013

Covariates	All Stages	Early Stage	Late Stage
	n (%)	n (%)	n (%)
Cases	10,109	8,735 (86.4)	1,374 (13.6)
Age			
18-34	957 (9.5)	836 (9.6)	121 (8.8)
35-64	5,732 (56.7)	4,951 (56.7)	781 (56.8)
>64	3,420 (33.8)	2,948 (33.7)	472 (34.4)
Gender			
Male	5,433 (53.7)	4,567 (52.3)	866 (63.0)
Female	4,676 (46.3)	4,168 (47.7)	508 (37.0)
Marital Status			
Married/Partner	4,450 (44)	3,803 (43.5)	647 (47.1)
Single	723 (7.2)	568 (6.5)	155 (11.3)
Widowed	578 (5.7)	495 (5.7)	117 (8.5)
Separated/Divorced	612 (6.1)	463 (5.3)	115 (8.4)
Unknown	3746 (37.1)	3,406 (39)	340 (24.7)
Year Diagnosed			
1995-1998	1,343 (13.3)	1,165 (13.3)	178 (13.0)
1999-2002	1,638 (16.2)	1,324 (15.2)	314 (22.9)
2003-2006	2,094 (20.7)	1,845 (21.1)	249 (18.1)
2007-2009	1,998 (19.8)	1,745 (20.0)	253 (18.4)
2010-2013	3,036 (30.0)	2,656 (30.4)	380 (27.7)
Anatomic Site			
Face, Head, Neck	1,898 (18.8)	1,666 (19.1)	232 (16.9)
Trunk	3,542 (35)	3,157 (36.1)	385 (28)
Limbs, Shoulder, Hips	4,328 (42.8)	3,886 (44.5)	442 (32.2)
Overlapping, NOS	341 (3.4)	26 (0.3)	315 (22.9)
Insurance			
Private insurance	4,820 (47.7)	4,175 (47.8)	645 (46.9)
Uninsured	364 (3.6)	260 (3.0)	104 (7.6)
Medicaid	334 (3.3)	233 (2.7)	101 (7.4)
Medicare	2,997 (29.6)	2,506 (28.7)	491 (35.7)
Unknown	1,594 (15.8)	1,561 (17.9)	33 (2.4)
Geography			
Urban	5,504 (54.4)	4,776 (54.7)	728 (53.0)
Rural	4,605 (45.6)	3,959 (45.3)	646 (47.0)
Geography			
Non-Appalachian	7,326 (72.5)	6,359 (72.8)	967 (70.4)
Appalachian	2,783 (27.5)	2,376 (27.2)	407 (29.6)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Poverty level	15.5% (6.6%)	15.4% (6.5%)	16.0% (7.1%)
Education level	74.5% (9.2%)	74.6% (9.2%)	73.8% (9.5%)
All MD per 10,000	21.6 (14.7)	21.7 (14.8)	20.9 (14.3)
FP MD per 10,000	3.03 (1.32)	3.03 (1.32)	3.00 (1.33)
Derm per 10,000	0.29 (0.30)	0.29 (0.30)	0.27 (0.30)

MD, medical doctor, includes all physicians including doctors of osteopathic medicine
FP, family practice; Derm, dermatologists

Figure 3.1 demonstrates the dramatic increase in early-stage melanoma between 1995 and 2013. The number of early-stage melanoma cases has steadily increased with a large increase in cases from 2003 to 2006 and the largest number of cases reported from 2010 to 2013. Further analysis of year groups 1995 to 2002 and 2003 to 2013 did not reveal a significant difference among these groups to explain the rise in early-stage cases. The number of late-stage melanomas has also steadily increased with a bump in the number of cases reported in 1999 to 2002 and the largest number of cases reported from 2010 to 2013. Of the 8,735 early-stage cases, 23.9% of the male and 21.6% of the females died. Of the 1,374 late-stage cases, 68.1% of the male and 61.8% of the females died.

Figure 3.1: Early and Late-Stage Melanoma by Year of Diagnosis in Kentucky from 1995-2013



The unadjusted odds ratios for late-stage melanoma are presented in table 3.2. Surprisingly, both of the geographic region variables and age are not significantly associated with late-stage melanoma lesions. Further analysis of each of these variables with stratification by year of diagnosis and pair-wise comparison again did not reveal an association. Females have a 36% (CI 0.57-0.72) decreased odds of late-stage melanoma compared to males. Meanwhile, being single has a 60% (CI 1.32-1.95) increased odds of late-stage melanoma compared to being married, whereas being separated or divorced has a 39% (CI

1.12-1.73) increased odds and being widowed has a 46% (1.17-1.82) increased odds. The year of diagnosis is significant only for the years of 1999-2002 having a 55% (1.27-1.90) increased odds of late-stage melanoma compared to 1995-1998. Interestingly, pair-wise comparison between year groups revealed no significant association between groups except for increased odds of late-stage disease for 1999-2002 compared to all other year groups. Interestingly, late-stage melanoma has a 18% (0.69-0.97) decreased odds for limbs, shoulder and hips lesions while there is a 87 times increased odds with overlapping or NOS lesions. Those people who are uninsured have a 2.59 (CI 2.03-3.30) times higher odds of late-stage melanoma compared to those who have private insurance while those with Medicaid have a 2.81 (CI 2.19-3.60) higher odds and those with Medicare have a 29% (CI 1.12-1.44) higher odds.

Poverty level, education level and density of dermatologists were each found to be significant in the univariate analysis. So, if a county had a 10% increase in percentage of the county in poverty there would be a 10% increased odds of late-stage melanoma. At the same time, if a county had a 10% decrease in percentage of the county that graduated from high school there would be a 10% increased odds of late-stage melanoma. While only 23 counties out of 120 have a dermatologist at all, we found that if a county added one dermatologist the odds of reporting a late-stage melanoma decreased by 23% (CI 0.64-0.93).

Table 3.2: Unadjusted Odds Ratio of Late-Stage Melanoma in Kentucky from 1995-2013.

Covariates	Late-Stage	Late-Stage
	OR (95% CI)	P value
Age		
18-34	Referent	
35-64	1.09 (0.89-1.34)	0.411
>64	1.11 (0.89-1.37)	0.355
Gender		
Male	Referent	
Female	0.64 (0.57-0.72)	<0.005
Marital Status		
Married/ Partner	Referent	
Single	1.60 (1.32-1.95)	<0.005
Separated/Divorced	1.39 (1.12-1.73)	0.001
Widowed	1.46 (1.17-1.82)	0.003
Unknown	0.59 (0.51-0.67)	<0.005
Year Diagnosed		
1995-1998	Referent	
1999-2002	1.55 (1.27-1.90)	<0.005
2003-2006	0.88 (0.72-1.09)	0.237
2007-2009	0.95 (0.77-1.17)	0.617
2010-2013	0.94 (0.77-1.13)	0.500
Anatomic Site		
Face, Head, Neck	Referent	
Trunk	0.88 (0.74-1.04)	0.134
Limbs, Shoulder, Hips	0.82 (0.69-0.97)	0.019
Overlapping, NOS	87.00 (57.00-132.79)	<0.005
Insurance		
Private insurance	Referent	
Uninsured	2.59 (2.03-3.30)	<0.005
Medicaid	2.81 (2.19-3.60)	<0.005
Medicare	1.29 (1.12-1.44)	<0.005
Unknown	0.14 (0.10-0.20)	<0.005
Geography		
Urban	Referent	
Rural	1.07 (0.96-1.2)	0.242
Geography		
Non-Appalachian	Referent	
Appalachian	1.13 (0.99-1.28)	0.062
Poverty level	1.01 (1.01-1.02)	0.002
Education level	0.99 (0.98-1.00)	0.007
All physicians	1.0 (0.99-1.0)	0.075
Family practice	0.99 (0.95-1.03)	0.583
Dermatologist	0.77 (0.64-0.93)	0.007

Analysis for interaction effect revealed interaction between age and gender and insurance and gender to be significant, refer to table 3.3. Females 35-64 years old and greater than 64 have 40% (CI 0.44-0.79) and 32% (CI 0.57-0.81) decreased odds of late-stage melanoma compared to females 18-34 years old. At the same time, males 35-64 years old have a 42% (CI 1.05-1.93) increased odds compared to females 18-34 years old. Also, compared to insured females, uninsured females, those on Medicare or with unknown insurance are all at increased odds of late-stage disease but those on Medicaid are at the highest risk with an over 11 (CI 6.56-19.93) fold odds. Meanwhile, the men uninsured, on Medicaid, Medicare or unknown insurance are at even higher odds of late-stage disease compared to insured females. Particularly, men on Medicaid are at a 20 (CI 12.26-35.38) fold increased odds and men on Medicare are at an almost 36 (CI 20.88-61.40) fold increased odds of late-stage melanoma.

Table 3.3: Interaction between Age and Gender and Insurance Status and Gender for Late-Stage Melanoma in Kentucky from 1995-2013.

	Female	**Male**
	OR (95% CI)	P value
Age		
18-34	Referent	0.84 (0.68-1.02)
35-64	0.60 (0.44-0.79)*	1.42 (1.05-1.93)*
>64	0.68 (0.57-0.81)*	1.15 (0.98-1.34)
Insurance		
Private insurance	Referent	0.64 (0.31-1.31)
Uninsured	4.61 (2.93-7.24)*	7.57 (4.84-11.82)*
Medicaid	11.44 (6.56-19.93)*	20.82 (12.26-35.38)*
Medicare	7.61 (4.25-13.64)*	35.80 (20.88-61.40)*
Unknown	6.80 (4.23-10.78)*	8.35 (5.32-13.09)*

* Indicates P value less than 0.05

The final model is displayed in table 3.4 and demonstrates that marital status, year diagnosed, anatomic site and insurance*gender are associated with late-stage melanoma. The final model explains 14.4% (Cox and Snell R square) and 26.3% (Nagelkerke R squared) of the variance in late-stage of diagnosis. A Hosmer-Lemeshow goodness of fit test was conducted and gave no indication of poor model fit at the 0.05 level (p value 0.081).

In the final model single people have a 39% (CI 1.11-1.75) increased odds of late-stage disease, widowed have a 44% (CI 1.11-1.89) increased odds and divorced people have a 36% (CI 1.06-1.75) increased odds compared to those who are married. As the incidence rate of melanoma increases from 1995 to 2013 the odds of late-stage diagnosis is significantly less from 2003 to 2013. Having a lesion that is overlapping or NOS increases the odds of late-stage disease 82 (CI 53.84-127.84) fold. Meanwhile, compared to privately insured females, being an uninsured female increases the odds of late-stage disease over 3 (CI 1.93-5.51) fold and being a female on Medicaid increased the odds over 7 (CI 4.08-14.31) fold. At the same time, men are at greater odds of late-stage melanoma compared to insured females with uninsured men at almost a 5 (CI 2.83-8.00) fold odds, men on Medicaid with almost a 12 (CI 6.36-21.59) fold odds and men on Medicare with a 19 (CI 10.35-35.63) times higher odds of late-stage disease compared to insured females. While the univariate analysis showed a significant impact of poverty, education and physician density on late-stage disease the adjusted regression did not show these outcome variables of interest to be significant.

Table 3.4: Final Model of Adjusted Odds Ratio of Late-Stage Melanoma in Kentucky from 1995-2013.

Covariates	Late-Stage	Late-Stage
	OR (95% CI)	P value
Marital Status		
Married/Partner	Referent	
Single	1.39 (1.11-1.75)	0.005
Widowed	1.44 (1.11-1.89)	0.007
Separated/Divorced	1.36 (1.06-1.75)	0.015
Unknown	0.73 (0.58-0.93)	0.008
Year Diagnosed		
1995-1998	Referent	
1999-2002	1.30 (1.00-1.68)	0.051
2003-2006	0.66 (0.48-0.90)	0.009
2007-2009	0.69 (0.50-0.94)	0.019
2010-2013	0.69 (0.51-0.93)	0.019
Anatomic Site		
Face, Head, Neck	Referent	
Trunk	0.92 (0.76-1.10)	0.343
Limbs, Shoulder, Hips	0.90 (0.75-1.07)	0.231
Overlapping, NOS	82.90 (53.84-127.84)	<0.005
Insurance*Gender		
Female Private insurance	Referent	
Female Uninsured	3.26 (1.93-5.51)	<0.005
Female Medicaid	7.64 (4.08-14.31)	<0.005
Female Medicare	4.66 (2.40-9.06)	<0.005
Female Unknown	4.08 (2.38-7.00)	<0.005
Male Private insurance	0.67 (0.31-1.44)	0.302
Male Uninsured	4.76 (2.83- 8.00)	<0.005
Male Medicaid	11.72 (6.36- 21.59)	<0.005
Male Medicare	19.2 (10.35-35.63)	<0.005
Male Unknown	5.03 (2.98-8.48)	<0.005

Discussion

Kentucky is a rural state with high poverty, low high school education levels and low physician density that has high melanoma incidence and mortality rates. Despite these factors this analysis did not find strong evidence to conclude that the stage of melanoma diagnosis is impacted by poverty, education or physician density. Instead, this analysis supports previous research that demonstrates that gender, marital status and health insurance status affect stage of diagnosis--indicating the population at highest risk for late-stage melanoma in Kentucky is unmarried males without insurance, on Medicaid or Medicare. [65,123,125]

This study found that Kentucky mirrors the US with 86.4% of lesions diagnosed as early-stage and the incidence rate rising dramatically over the last few decades. [7] The upswing in early-stage cases in Kentucky begins in 2003 with no obvious explanation. In 2002 the AJCC did publish an updated staging manual that included tumor thickness and ulceration in the T category. [17] It is possible that this change in staging could increase the number of lesion considered early-stage but would not account for the continued surge still seen today. Instead, this continued increase is most likely attributed to our aging population, increased screening, increased recreational UV exposure and increased tanning bed use. [2,6,14,17,59,62]

As expected, the majority of cases were male but the average overall age was younger, 56.9 years, than the national average of 63 years. [7] Interestingly, the location of the lesion remained important as lesions on the limbs, shoulders

and hips had a slight increase in late-stage disease compared to early-stage in the univariate analysis, but astonishingly in the final model the overlapping lesion or lesion NOS had an 83 times higher odds of late-stage disease. The influence of geographic region such as, rural or Appalachia residence was not associated with a greater odds of being a late-stage case. Yet, having a spouse or partner was clearly protective from being diagnosed with late-stage melanoma. This supports previous research by Mandala et al that marriage is protective against later stage melanoma with those who are widowed at particularly increased risk.[123]

In a nation that does not provide affordable health care without insurance it is not unexpected that being uninsured or having Medicaid increases the odds of late-stage melanoma. The analysis of interaction emphasizes the importance and complexity of insurance by noting that females and males on Medicaid are at increased odds of late-stage diagnosis. While at the same time, males with Medicare are at dramatically increased odds of late-stage disease compared to females with private insurance.

Education and poverty level by county was utilized to measure the effect of SES on late-stage melanoma. Increased poverty and decreased education was noted to be associated with late-stage disease in the univariate analysis but this paper did not find an association in the final model when controlling for all other variables. Physician density by county was significant for dermatologists in the univariate analysis but not in the final model.

This study has several important limitations. First, poverty and education were used as surrogates for socioeconomic status and were measured at the county level, not the individual level. Yet, the use of aggregate measures of socioeconomic status has been validated by other studies. [29-31] Secondly, physician density can only be considered an aggregate of patients' use of medical services. The actual use of physician services by these patients may not be reflective of the physician density. Additionally, this study did not account for other medical providers including physician assistants and nurse practitioners. The analysis of poverty level, education level and physician density by county in a state with 120 counties may have been a too finite breakdown of the data. Further research should consider analysis by larger geographic regions. Lastly, this study was restricted to the state of Kentucky, which may not be representative of other parts of the country.

As the rate of melanoma continues to increase, this study shows that Kentucky needs to focus preventative health measures towards unmarried men who do not have private insurance, especially those with Medicare. Since this analysis did not demonstrate any influence of poverty or education at the county level, further research needs to be conducted with individual level data. Additionally, the effect of health insurance status on melanoma disease stage seen in this analysis lends itself to further investigation. Of interest would be the effect of the recent expanded health insurance access through the Affordable Care Act that has provided over 500,000 uninsured Kentucky residents with coverage. [162]

Kentucky is a rural state with high poverty, lower than average education levels and low physician density but it appears that these factors have not impacted melanoma stage of diagnosis. Instead this study supports previous research that indicates that public health measures should focus on unmarried men who are uninsured or on Medicaid or Medicare. [21,74,125]

Chapter IV

Individual and Social Factors Associated with Non-standard Surgical Treatment For Early-stage Melanoma in Kentucky

Introduction

Over the last three decades the incidence of melanoma has doubled in the United States (US) while the mortality rate has remained stable. [3] The prognosis for melanoma is excellent with a 98% 5-year survival rate for early-stage disease.[7] Consequently, early diagnosis and complete removal of the lesion is paramount as local recurrence is associated with the development of systemic metastasis and a poor prognosis of less than a 5% chance of survival at 10 years. [131]

As the incidence of melanoma increases the number of clinicians providing treatment increases which makes the need for treatment guidelines paramount. [22,128] The National Comprehensive Cancer Network (NCCN) provides evidence-based consensus-driven guidelines by cancer type to help guide clinicians. [163] The NCCN melanoma treatment guidelines state that the primary and potentially curative treatment for early-stage melanoma is wide local excision to completely remove the lesion with clear margins. [47] Clear margins are defined as the edge or border of the tissue that is removed around a cancer that is found to be without cancer cells by the pathologist. [164] At least 1 cm and no more than 2 cm of clear surgical margins is recommended. [47,51,130] No residual tumor is considered the standard of care treatment that should be provided to all patients unless not appropriate based on their unique medical situation. [47]

Despite the specific treatment guidelines from the NCCN, evidence suggests that melanoma surgical guidelines are followed approximately half of the time. [28] The effect of this non-standard treatment is unclear because the association between inadequate margins and mortality has not been confirmed but continued morbidity can be inferred because several studies have established that inadequate surgical margins are correlated with local recurrence.[51,53,54,58,134,] Therefore, the current belief is that as inadequate margins increase the risk of local reoccurrence it may also be associated with increased mortality. [53-55]

Although each medical situation varies, this level of variation in adherence to medical guidelines for melanoma treatment may be a symptom of inequity in health care delivery. While there are many papers on the risk factors that influence melanoma incidence and mortality the literature on surgical treatment is anemic. At this time, the research indicates that those less likely to be provided the standard of care surgical treatment have an early-stage lesion, are older, minority race, not married, resided in rural areas and the lesion is on their head or neck. [28,53,54,85,123,132,143,145-148]

A study by Al-Quaryshi et al also noted that patients with low annual incomes or on Medicaid were more likely to be treated by a low-volume surgeon.[144] At the same time these low-income patients were more likely to be treated in a non-teaching, rural or low-volume hospital. [144] Additionally, an analysis of disparities in cancer care in West Virginia noted that residing in rural

Appalachia itself has been associated with later stage cancer diagnoses, variance in treatment and survival. [165]

Differences in melanoma treatment have also been associated with physician specialty, where they work in the healthcare system and their practice patterns. [85,149] Rivard et al found that when comparing the referral cancer center to outside centers that the referral cancer center more commonly followed surgical guidelines for sentinel lymph node biopsy but less commonly for wide surgical excision. [149] While melanoma surgical treatment adherence has not been linked to physician density, access to family practice physicians and dermatologists is associated with earlier stage diagnosis while access to dermatologists is associated with lower mortality. [22,128]

Kentucky is an excellent population to study adherence of melanoma surgical treatment guidelines because of the high rate of melanoma in the state with a majority white population. Also, the high poverty rate, wide range in education levels, low physician density, rural and Appalachian geography makes this an ideal place to investigate the effect of these social determinants of health on early-stage melanoma treatment.

The purpose of this paper is to assess for any associations between individual and social factors on treatment provided to early-stage melanoma in white non-Hispanic Kentuckians from 1995 to 2013. We hypothesize that non-standard treatment more frequently occurs in rural and Appalachian regions and geographic areas with lower physician density and lower socioeconomic status (SES) as indicated by an increase in poverty level and decrease in education

level. This study intends to lend insight into the factors associated with non-standard surgical treatment for early-stage melanoma in Kentucky, which in turn could provide an avenue for public health intervention.

Methods

Study population and data resources

The Kentucky Cancer Registry (KCR) provided data on individual level variables while the United States Census Bureau and the Kentucky Department of Public Health delivered the community level variables. Early-stage melanoma cases from non-Hispanic whites, 18 years or older from 1995 to 2013 were gathered; insitu lesions and non-primary tumors were excluded. Early-stage was defined as stage I and stage II. Due to minimal cases in other race groups only non-Hispanic whites were included. Cases without treatment data were excluded. This provided data on 8,532 cases with individual data on age, gender, marital status, year of diagnosis, anatomic site of lesion, health insurance status, and geographic region of rural/urban and Appalachian/non-Appalachian.

The percentage of each county with high school education and percentage below the poverty level was collected from the 2000 United States Census Bureau. [8,11] Meanwhile, the 2006 physician licensure data with the number of all-physicians, family practice physicians and dermatologists in each county was provided by the Kentucky Department of Public Health. [12] Physician density was calculated with the number of all-physicians, family physicians and dermatologists, per 10,000 population by county using the 2006 US Census Bureau intercensal population estimates. [159]

Outcome and Independent Variables

The outcome variable of interest--standard of care treatment--was formed into a dichotomous variable of yes/no. Standard of care treatment was defined as surgical margin code 0 which is no residual tumor with all margins grossly and microscopically negative. Non-standard of care treatment was defined as surgical margin codes 1-9 which includes residual tumor, microscopic residual tumor, macroscopic residual tumor, margins not evaluable, no surgical removal of the primary site and unknown. [166]

The independent variables of interest are geographic region, poverty level, education level and physician density. Geographic region is defined with two variables: rural/urban and Appalachian/non-Appalachian. Urban is defined as Beale codes 1 through 3 while rural is defined as Beale codes 4 through 9. Non-Appalachian is defined by counties defined as non-Appalachian. [160] Poverty level was categorized into three groups based upon the mean of 15.5% with high as greater than 20% of population in poverty, intermediate as 10 to 20% of population in poverty and low as less than 10% of population in poverty. Education level was categorized into three groups with less than 70% with high school education level defined as low education, 70 to 80% as intermediate education, and greater than 80% as high education.

Physician density per 10,000 population per county was defined by the following three categories: all physicians, family practice physicians and dermatologists. All physicians was applied as melanoma is diagnosed and treated by many types of physicians not only family practice physicians and

dermatologists. All Kentucky physicians were categorized into three groups based upon a mean of 21.68 physicians per 10,000 population with high indicating greater than 25 physicians, intermediate indicating counties with 12 to 25 physicians and low for counties with less than 12 physicians. Family practice physicians were categorized into three groups as well based on a mean of 3.03 physicians per 10,000 population with high indicating greater than 3.10 physicians, intermediate indicating 2.6 to 3.09 physicians and low indicating less than 2.6 family practice physicians. Dermatologist were also categorized into three groups with a mean of 0.29 physicians with high indicating greater than 0.65 dermatologists per 10,000 population, intermediate indicating 0.11 to 0.65 dermatologists and low indicating less than 0.10 dermatologists.

The year of diagnosis was categorized into five groups with 1995 to 1998, 1999 to 2002, 2003 to 2006, 2007 to 2009 and 2010 to 2013. Gender was categorized with male and female. Age was categorized into three groups with 65 and older, 64 to 35 and 34 to 18 years. Marital status is also categorical with married/partner, single, widow, separated/divorced and unknown. Health insurance status was categorized by primary payor type as private insurance, uninsured, Medicaid, Medicare and unknown. Anatomic site of the lesion was categorized based upon the area of the body.

Statistical Analysis

Descriptive statistics were used to describe the study population and the distribution of variables for all cases, standard treatment and non-standard

treatment. A graph exhibiting melanoma treatment non-adherence from 1995 to 2013 was created.

Logistic regression was used to assess the unadjusted associations between each covariate and non-standard treatment. Covariates include age at diagnosis, gender, marital status, year diagnosed, anatomical site of lesion, health insurance status, urban/rural, non-Appalachian/Appalachian, poverty level, education level and physician population ratio for all-physicians, family practice physicians and dermatologists. The resultant estimated odds ratios (OR) and 95% confidence interval were described. Each significant variable was assessed for interaction and significant interaction terms were described. These significant interaction terms were then utilized in the final model.

Multiple logistic regression was used to formulate the final model of the non-standard treatment group. The model was first run with all covariates then variables were removed using backward elimination to find the model of best fit. All reported P values are two-tailed. Statistical significance was set at an alpha level of .05. All analyses were conducted using SPSS version 23. [161]

Results

Of the 8,532 cases, 5,099 (59.8%) were provided the recommended standard of care treatment for their early-stage melanoma lesion, leaving 3,433 cases with non-compliant treatment. Refer to table 4.1. The mean age of all early-stage cases is 56.8 years with a standard deviation of 16.2 years and range of 18 to 102 years old. For both the standard treatment and non-standard treatment groups the majority of cases were 35 to 64 years old. While most of the

all cases group were married, 37.7% of cases had an unknown marital status. For the non-standard treatment group the percentage of unknown marital status rose to 44.1% while the married group comprised only 39.5% of cases. Exploratory analysis demonstrated that unknown marital status was not differentially distributed with other variables therefore; the variable of marital status was not evaluated further in the analysis.

The number of early-stage cases has increased by over two-fold from 1995 to 2013. At the same time the percentage of cases that are non-standard treatment have significantly increased compared to the standard treatment group. The majority of lesions in the standard and non-standard treatment groups were found on the limbs, shoulders and hips. In the standard treatment group 57.4% of cases had private insurance while in the non-standard treatment group only 35.9% had private insurance. The standard and non-standard treatment groups are similar with the bulk residing in urban and non-Appalachian regions.

The mean percentage of poverty level by county for all cases is 15.5% with a standard deviation of 6.5% and range of 4.1% to 45.4%. The standard treatment and non-standard treatment groups are similar in poverty levels with the non-standard group having a slightly higher percentage of cases in the high and low poverty levels. The mean percentage of high school education level by county for all cases is 74.5% with a standard deviation of 9.2% and range of 49.2% to 86.5%. All three groups were similar with each group having greater than 40% of cases at a high level of education.

The state of Kentucky has 9,109 physicians, 1,361 family practice physicians and 121 dermatologists. There is a wide range of all physicians with zero to 56.5 per 10,000 population per county. Comparing the standard and non-standard treatment groups the physician density is similar. Meanwhile, the number of family practice physicians per 10,000 population per county has a limited range of 0 to 7.7 but significant variation between the standard and non-standard treatment groups. With the non-standard treatment group having 37.8% of cases from counties with high family practice physician density. While the majority of counties do not have a dermatologist, the range of dermatologists per 10,000 population is only 0 to 0.93. Comparing treatment groups there are less non-standard treatment cases coming from counties with high dermatologist density.

Table 4.1, Characteristics of Melanoma Cases by Treatment in Kentucky from 1995-2013

Covariates	All Cases	Standard Treatment	Non-Standard Treatment
	n (%)	n (%)	n (%)
Cases	8,532 (100.0)	5,099 (59.8)	3,433 (40.2)
Age			
18-34	816 (9.6)	517 (10.1)	299 (8.7)
35-64	4,849 (56.8)	2,993 (58.7)	1,856 (54.1)
>65	2,867 (33.6)	1,589 (31.2)	1,278 (37.2)
Gender			
Male	4,464 (52.3)	2,634 (51.7)	1,830 (53.3)
Female	4,068 (47.7)	2,465 (48.3)	1,603 (46.7)
Marital Status			
Married	3,792 (44.4)	2,432 (47.7)	1,360 (39.6)
Single	568 (6.7)	354 (6.9)	214 (6.2)
Widowed	458 (5.4)	278 (5.5)	180 (5.2)
Separated/Divorced	495 (5.8)	331 (6.5)	164 (4.8)
Unknown	3,219 (37.7)	1,704 (33.4)	1,515 (44.1)
Year Diagnosed			
1995-1998	1,155 (13.5)	1,009 (19.8)	146 (4.3)
1999-2002	1,319 (15.5)	1,220 (23.9)	99 (2.9)
2003-2006	1,839 (21.6)	1,117 (21.9)	722 (21)
2007-2009	1,711 (20.1)	814 (16)	897 (26.1)
2010-2013	2,508 (29.4)	939 (18.4)	1,569 (45.7)
Anatomic Site			
Face, Head, Neck	1,620 (19.0)	898 (17.6)	722 (21)
Trunk	3,074 (36.0)	1,848 (36.2)	1,226 (35.7)
Limbs, Shoulder, Hips	3,815 (44.7)	2,340 (45.9)	1,475 (43)
Overlapping, NOS	23 (0.3)	13 (0.3)	10 (0.3)
Insurance			
Private insurance	4,157 (48.7)	2,926 (57.4)	1,231 (35.9)
Uninsured	260 (3.0)	181 (3.5)	79 (2.3)
Medicaid	233 (2.7)	163 (3.2)	70 (2.0)
Medicare	2,492 (29.2)	1,679 (32.9)	813 (23.7)
Unknown	1,390 (16.3)	150 (2.9)	1,240 (36.1)
Geography			
Urban	4,640 (54.4)	2,775 (54.4)	1,865 (54.3)
Rural	3,892 (45.6)	2,324 (45.6)	1,568 (45.7)
Geography			
Non-Appalachian	6,189 (72.5)	3,784 (74.2)	2,405 (70.1)
Appalachian	2,343 (27.5)	1,315 (25.8)	1,028 (29.9)

Table 4.1, continued

Covariates	All Cases	Standard Treatment	Non-Standard Treatment
	n (%)	n (%)	n (%)
Poverty level			
Low	1,145 (13.4)	582 (11.4)	563 (16.4)
Intermediate	5,804 (68.0)	3,590 (70.4)	2,214 (64.5)
High	1,583 (18.6)	927 (18.2)	656 (19.1)
Education level			
High	3,608 (42.3)	2,167 (42.5)	1,441 (42.0)
Intermediate	2,436 (28.6)	1,470 (28.8)	966 (28.1)
Low	2,488 (29.2)	1,462 (28.7)	1.026 (29.9)
All physicians			
High	3,092 (36.2)	1,870 (36.7)	1,222 (35.6)
Intermediate	2,696 (31.6)	1,579 (31.0)	1,117 (32.5)
Low	2,744 (32.2)	1,650 (32.4)	1,094 (31.9)
Family practice physicians			
High	2,810 (32.9)	1,511 (29.6)	1,299 (37.8)
Intermediate	2,860 (33.5)	1,835 (36.0)	1,025 (29.9)
Low	2,862 (33.5)	1,753 (34.4)	1,109 (32.3)
Dermatologists			
High	2,230 (26.1)	1,367 (26.8)	863 (25.1)
Intermediate	2,543 (29.8)	1,465 (28.7)	1,078 (31.4)
Low	3,759 (44.1)	2,267 (44.5)	1,492 (43.5)

Figure 4.1 demonstrates the dramatic increase in the number of early-stage melanoma lesions provided non-standard treatment between 1995 and 2013. From 1995 to 2002 less than 50 cases per year received non-standard treatment. In 2003 the number rose to 60 then jumped to 247 in 2005 and by 2012 over 400 cases received non-standard treatment.

Figure 4.1, Number of Early-Stage Cases with Non-Standard Treatment by Year in Kentucky from 1995-2013

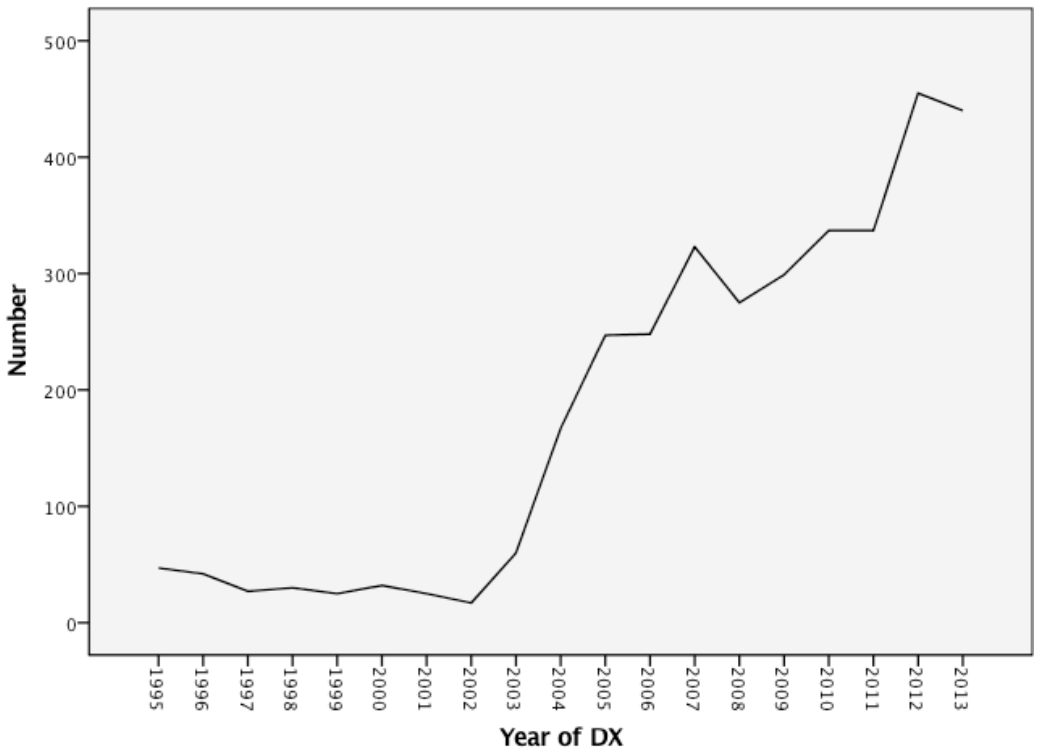
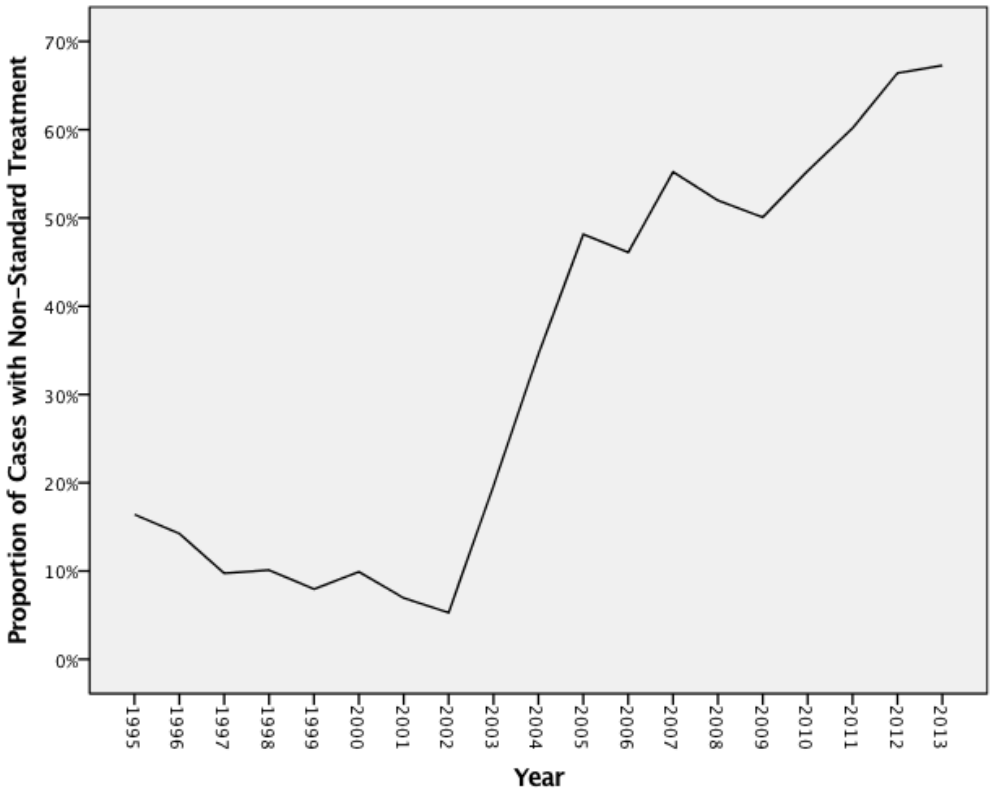


Figure 4.2 shows the proportion of early-stage lesions from 1995 to 2013 that received non-standard treatment. From 1995 to 2003 less than 20% of cases received non-standard treatment then interestingly, this proportion increased dramatically with 48% in 2005 and 67% in 2013.

Figure 4.2, Proportion of Early-Stage Cases with Non-Standard Treatment by Year in Kentucky from 1995-2013



The unadjusted odds ratios for non-standard treatment compared to standard treatment of early-stage melanoma are presented in table 4.2. Interestingly, gender was not significant for non-standard treatment but age greater than 64 years was found to increase the odds of non-standard treatment by 39% (CI 1.16-1.63) compared to people aged 18 to 34. The year the melanoma lesion was diagnosed was significant for non-standard treatment with the odds increasing dramatically. The lesions diagnosed from 2010 to 2013 have

an 11.55 (9.54-13.98) times increased odds of non-standard treatment compared to the lesions diagnosed from 1995 to 1998.

The anatomical site of a melanoma lesion also significantly effects the treatment with a lesion on the trunk, limbs, shoulders or hips with a decreased odds of non-standard treatment compared to the face, head or neck. Insurance status is not significant for non-standard treatment except for unknown insurance status, which has a 19.65 (16.38-23.57) times higher odds of non-standard treatment compared to private insurance.

Remarkably, the unadjusted variables of urban vs. rural geography, education level and all physician density are not significantly associated with non-standard treatment. Now, residing in Appalachia does increase the odds of non-standard treatment by 23% (1.12-1.35) compared to residing in non-Appalachia. Yet, surprisingly the odds of non-standard treatment is less likely in counties with higher poverty where they are 27% (0.63-0.85) less likely to receive non-standard treatment compared to those in low poverty level counties. Also interesting, the odds of non-standard treatment lessen as the family practice physician density decreases. At the same time, intermediate density for dermatologists has a 17% (1.04-1.31) increased odds of non-standard treatment compared to high-density counties.

Table 4.2, Unadjusted Odds Ratio of Melanoma Non-Standard Treatment cases in Kentucky, 1995-2013

Covariates	Non-Standard Treatment	Non-Standard Treatment
	OR (95% CI)	P value
Age		
18-34	Referent	
35-64	1.07 (0.92-1.25)	0.374
>64	1.39 (1.16-1.63)	<0.005
Gender		
Male	Referent	
Female	0.94 (0.86-1.02)	0.135
Year Diagnosed		
1995-1998	Referent	
1999-2002	0.56 (0.43-0.73)	<0.005
2003-2006	4.47 (3.67-5.44)	<0.005
2007-2009	7.62 (6.25-9.28)	<0.005
2010-2013	11.55 (9.54-13.98)	<0.005
Anatomic Site		
Face, Head, Neck	Referent	
Trunk	0.83 (0.73-0.93)	0.002
Limbs, Shoulder, Hips	0.78 (0.70-0.88)	<0.005
Overlapping, NOS	0.96 (0.42-2.20)	0.917
Insurance		
Private insurance	Referent	
Uninsured	1.04 (0.79-1.36)	0.792
Medicaid	1.02 (0.77-1.36)	0.889
Medicare	1.15 (1.03-1.28)	0.010
Unknown	19.65 (16.38-23.57)	<0.005
Geography		
Urban	Referent	
Rural	1.00 (0.92-1.10)	0.930
Geography		
Non-Appalachian	Referent	
Appalachian	1.23 (1.12-1.35)	<0.005
Poverty level		
Low	Referent	
Intermediate	0.64 (0.56-0.72)	<0.005
High	0.73 (0.63-0.85)	<0.005
Education level		
High	Referent	
Intermediate	0.99 (0.89-1.10)	0.825
Low	1.06 (0.95-1.17)	0.310

Table 4.2, continued

Covariates	Non-Standard Treatment	Non-Standard Treatment
	OR (95% CI)	P value
All physicians		
High	Referent	
Intermediate	1.08 (0.97-1.20)	0.140
Low	1.02 (0.91-1.13)	0.787
Family practice physicians		
High	Referent	
Intermediate	0.65 (0.58-0.72)	<0.005
Low	0.74 (0.66-0.82)	<0.005
Dermatologists		
High	Referent	
Intermediate	1.17 (1.04-1.31)	0.010
Low	1.04 (0.94-1.17)	0.447

Table 4.3 shows the significant interaction terms of Appalachian geography and family practice physicians with poverty and family practice physicians. In counties with high density of family practice physicians, Appalachian areas have 36% (CI 0.55-0.75) lower odds of non-standard treatment compared to non-Appalachian areas. Whereas, when comparing non-Appalachian areas low family practice physician density decreases the odds of non-standard treatment by 33% (CI 0.58-0.77) compared to high physician density counties. Notably, the interaction of poverty level and family practice physicians is significant for high-density family practice physicians where high poverty level counties have 147% (1.95-3.10) higher odds of non-standard treatment compared to low poverty level counties.

Table 4.3, Interaction between Geography and Family Practice Physicians and Poverty Level and Family Practice Physicians for Non-Standard Treatment in Kentucky from 1995-2013

	FP High	FP Intermediate	FP Low
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Geography			
Non-Appalachian	Referent	1.13 (0.98-1.30)	0.67 (0.58-0.77)*
Appalachian	0.64 (0.55-0.75)*	0.92 (0.77-1.10)	0.92 (0.69-1.22)
Poverty level			
Low	Referent	1.17 (0.86-1.58)	1.21 (0.98-1.51)
Intermediate	1.27 (1.06-1.52)*	0.83 (0.70-0.98)*	0.92 (0.77-1.10)
High	2.47 (1.95-3.10)*	1.25 (0.90-1.24)	0.98 (0.77-1.24)

* Indicates P value less than 0.05
FP, family practice physician

The final model was significant for the variables of interest: Appalachian geography, poverty level with family practice physician density and physician density. Refer to table 4.4. The final model explains 32.1% (Cox and Snell R square) and 43.4% (Nagelkerke R squared) of the variance in non-standard treatment.

Early-stage melanoma lesions in those older than 64 years old are at a 40% (CI 1.09-1.79) increased odds of non-standard treatment compared to those aged 18 to 34. Comparing the year diagnosed, from 2003 to 2013 the odds of non-standard treatment has increased dramatically. In 2003 to 2006 there was an almost 3 (CI 2.41-3.68) fold increase odds of non-standard therapy followed by a 5.77 (CI 4.67-7.12) fold increase odds of non-standard therapy in 2007 to 2009 and by 2010 to 2013 there was an over 9 (CI 7.41-11.10) fold increase odds of non-standard therapy compared to the cases in 1995 to 1998.

Lesions on the trunk, limbs, shoulders or hips have a 29% (CI 0.61-0.83) decreased odds of non-standard treatment compared to lesions on the face, head or neck. Insurance through Medicare is protective against non-standard treatment with a 24% (CI 0.63-0.91) decreased odds compared to private insurance while unknown insurance increases the odds over 15 (CI 12.50-18.79) fold. Demographics of the unknown insurance group are similar to all other cases except that 94% of unknown insurance group cases also had unknown marital status.

While controlling for all other variables in the model, Appalachian geography and physician density are significant for non-standard treatment. Residing in an Appalachian area increases the odds of non-standard treatment 2 (CI 1.67-2.52) fold compared to residing in non-Appalachia. Residing in a county with low all-physician density increases the odds of non-standard treatment by 34% (CI 1.05-1.72) but surprisingly low dermatologist density decreases the odds of non-standard treatment by 38% (CI 0.46-0.82).

The interaction between family practice physicians and poverty level remained significant in the final model highlighting the effect of high-density family practice physicians and poverty level. Counties with high and intermediate poverty and high family practice physician density have a 99% (CI 1.49-2.66) and 72% (CI 1.16-2.53) increased odds of non-standard treatment compared to counties with low poverty and low family practice physician density.

Table 4.4, Final Model of Adjusted Odds Ratio of Melanoma Non-Standard Treatment cases in Kentucky, 1995-2013

Covariates	Non-Standard Treatment	Non-Standard Treatment
	OR (95% CI)	P value
Age		
18-34	Referent	
35-64	0.99 (0.83-1.21)	0.988
>64	1.40 (1.09-1.79)	0.009
Year Diagnosed		
1995-1998	Referent	
1999-2002	0.47 (0.36-0.63)	<0.005
2003-2006	2.98 (2.41-3.68)	<0.005
2007-2009	5.77 (4.67-7.12)	<0.005
2010-2013	9.07 (7.41-11.10)	<0.005
Anatomic Site		
Face, Head, Neck	Referent	
Trunk	0.71 (0.61-0.83)	<0.005
Limbs, Shoulder, Hips	0.71 (0.61-0.82)	<0.005
Overlapping, NOS	2.23 (0.88-6.08)	0.090
Insurance		
Private insurance	Referent	
Uninsured	1.00 (0.74-1.36)	0.981
Medicaid	0.86 (0.63-1.19)	0.360
Medicare	0.76 (0.63-0.91)	0.004
Unknown	15.33 (12.50-18.79)	<0.005
Geography		
Non-Appalachian	Referent	
Appalachian	2.05 (1.67-2.52)	<0.005
All physicians		
High	Referent	
Intermediate	1.24 (0.99-1.54)	0.057
Low	1.34 (1.05-1.72)	0.017
Dermatologists		
High	Referent	
Intermediate	0.58 (0.45-0.74)	<0.005
Low	0.62 (0.46-0.82)	<0.005
Poverty level & FP physicians		
Low poverty, high density	Referent	
Low poverty, interm density	0.88 (0.61-1.28)	0.501
Low poverty, low density	0.99 (0.75-1.31)	0.945
Interm poverty, high density	1.99 (1.49-2.66)	<0.005
Interm poverty, interm density	1.11 (0.80-1.53)	0.528
Interm poverty, low density	1.13 (0.85-1.49)	0.404
High poverty, high density	1.72 (1.16-2.53)	0.007
High poverty, interm density	1.75 (1.11-2.76)	0.015
High poverty, low density	1.25 (0.87-1.80)	0.230

FP, family practice physician

Discussion

This study found that 40% of early-stage melanoma lesions did not receive the standard of care surgical treatment, which mirrors the findings from previous studies. [28,85,142,143,] While the number of melanoma cases has steadily increased over time, it is striking that the proportion of cases receiving non-standard surgical treatment has dramatically increased overtime from a low of 5.3% of cases in 2002 to a high of 67.3% of cases in 2013. This reinforced previous studies that have demonstrated a trend of decreasing compliance with wide local excision recommendations over the recent decades.[130,142,143] The cause for this is unclear but this level on non-adherence to surgical guidelines may be a symptom of health disparities.

As expected from previous research findings, the final model found increased odds of non-standard surgical treatment with older age and head or neck lesions. [53] Of interest, Medicare insurance was protective against non-standard treatment while unknown insurance had a 15 fold increased odds. Improved collection of this variable is necessary to better understand this group.

Interestingly, residing in Appalachian itself increased the odds of non-standard treatment. This matches research that has found an increase in non-standard cancer treatment in Appalachia for breast, lung and prostate cancer. [167-169] For example, an analysis of lung cancer treatments in West Virginia noted non-compliant treatment in 46.5% of the cases.[168]

The effect of physician density is fascinating as the final model indicates that low all-physician density increases the odds of non-standard therapy while

low dermatologist density decreases the odds. It must be noted that there are only 121 dermatologists in the state of Kentucky and only 21 out of 120 counties with a dermatologist. Therefore, dermatologist density must be further studied while the finding of increased odds for non-standard treatment associated with low all-physician density likely holds more weight. This supports the assertion that increasing access to health care through all physicians is critical in melanoma care.

Earlier research has analyzed the effect of physician density on melanoma stage of diagnosis and mortality but this is the first to evaluate treatment adherence. [22] It must be pointed out that physician density in this study does not indicate where each person received treatment, as it is quite possible that patients left their county for melanoma treatment by a dermatologist or melanoma specialist. Also, physician density can only be considered an aggregate of patients' use of medical services. The actual use of physician services by these patients may not be reflective of the physician density. Additionally, this analysis of physician density provides no insight into physician practice patterns or the utilization of non-physician clinicians including physician assistants and nurse practitioners.

The interaction between poverty level and family practice physicians highlights the relationship between poverty and access to medical care. In counties of high family practice physician density if the county also had a high poverty level there was a significant increase in non-standard treatment compared to low poverty counties. This demonstrates that providing physicians

alone is not the answer to standard melanoma treatment but that poverty itself plays a role. This reinforces other papers that have demonstrated an association between socioeconomic status and melanoma incidence, mortality and chemotherapy treatment. [6,20,144]

Compliance with melanoma surgical guidelines is not expected to be 100% as the patient specific needs have priority over general guidelines. Reasons for noncompliance are many and it is likely that there are appropriate medical reasons for non-standard surgical treatment present in several of these cases. That being said, 40% noncompliance is high and while physician and patient preference during treatment discussions is difficult to study this study lends some insight into which patients may be vulnerable. This analysis defines the vulnerable patient as one who is older than 65 years with a head or neck lesion, and with unknown insurance status. Additionally, those residing in Appalachia, a county with low all-physician density or a county with high or intermediate poverty with high family practice density and high dermatologist density are susceptible.

This paper demonstrates that the incidence of non-standard treatment is increasing in Kentucky and it is not clear who is providing this treatment. It is known that as the incidence of melanoma increases, the care for these deadly lesions spreads beyond dermatologists to clinicians who do not care for a large number of melanoma patients, attend multidisciplinary conferences or receive relevant continued medical education. [170] Previous studies have noted that increased compliance with surgical guidelines is associated with surgeons who care for more melanoma cases. [143,171]

To increase compliance with melanoma surgical guidelines it has been recommended to develop metrics that record and monitor the following of melanoma surgical guidelines nationally. [170] Since patients are often referred to a melanoma specialist following treatment that did not follow the guidelines, Wasif et al recommended regionalization of melanoma treatment as is done for some other cancer types to increase compliance. [53,170] It could also be argued that although the guidelines are published and disseminated that there needs to be a concerted effort to better educate all clinicians especially those in Appalachia, counties with low all-physician density or high poverty. Additionally, clinicians need to be made aware of those patients that are at higher odds of receiving non-standard treatment. Lastly, patient education on melanoma treatment guidelines may empower patients in the physician-patient discussion of treatment options.

There are limitations to this study that need to be considered when interpreting the findings. The primary limitation is the utilization of county level data for poverty and education that were used as surrogates for socioeconomic status. Although, the use of aggregate measures of socioeconomic status has been validated by other studies it still cannot replace individual level data. [29-31] Although this study utilized cancer registry data that is regarded for its quality, it must be pointed out that the margins recorded are pathological and not clinical. It is known that there is shrinkage of the lesion, 10-20%, following histologic processing that would affect the recorded margin. [172] This study utilized surgery codes with no residual tumor as the definition of standard of care to avoid this

limitation but this effect is still possible. While this limitation is noted it would not account for this degree of noncompliance. [53]

Another limitation is the analysis of poverty level, education level and physician density by county in a state with 120 counties. This may have been too fine of a categorization of the data and further research should consider analysis by larger geographic regions. Lastly, this study was restricted to the state of Kentucky, which may not be representative of other parts of the country.

While there is vast amounts of literature on other aspects of melanoma the literature on treatment adherence is limited. Further research should be guided by a need to better understand the variables pertaining to both the patient and physician in melanoma treatment decisions. Analysis of non-compliance by type of provider could lend insight into who is less likely to follow guidelines. Additionally, future research needs to evaluate the cost of under treatment and how to provide the highest quality of care to the largest number of melanoma patients.

To determine the effect of non-adherence, further analysis is needed with long term follow up to evaluate for the effects of morbidity and mortality. For example, over the last few decades while the incidence of melanoma has increased in the US from 7.9 cases per 100,000 population in 1975 to 24.0 cases in 2013, the mortality rate for melanoma has remained steady at 2.7 deaths per 100,000 population. [157] In Kentucky, the incidence of melanoma has also increased from 22.1 cases per 100,000 population in 1995 to 24.3 cases in 2013. However, the mortality rate has also increased from 2.5 cases per 100,000

population in 1994 to 3.4 cases in 2013. If the Kentucky mortality rates could be lowered to the national rates this would result in approximately 30 fewer melanoma deaths in Kentucky per year. [157] Therefore, further research should investigate the increasing non-compliance of surgical guidelines and the association with this high mortality rate.

This analysis determined that 40% of early-stage melanoma lesions in Kentucky were provided non-standard treatment and that the rate of non-standard surgical treatment is on the rise. This is a public health concern that needs intervention. Additionally, this study confirmed that those at increased odd of non-standard treatment live in Appalachia, a county with low all-physician density or a county with high poverty and high family practice physician density. The state of Kentucky needs to implement policy that increases patient access to melanoma care and educates clinicians to halt the trend of increasing non-standard melanoma treatment.

Chapter V

Conclusion

This capstone attempted to quantify the association of individual and social factors on melanoma late-stage diagnosis and non-adherence to surgical treatment guidelines in Kentucky. Figure 1.1, presented in Chapter 1, depicts the variables analyzed in this capstone that could affect both disease stage of diagnosis and surgical treatment provided. The purpose of this concluding chapter is to summarize the findings of the preceding chapters, discuss the implications of these studies for public health and to summarize the limitations and recommendations. This work was intended to identify future public health avenues to decrease late-stage diagnosis and non-adherence to melanoma surgical treatment guidelines.

Summary of Findings

In chapter 3, the first paper hypothesized that late-stage lesions occur more frequently in geographic areas with lower physician density and lower socioeconomic status (SES) as indicated by an increase in poverty level and decrease in education level. The analysis of melanoma lesions from 1995 to 2013 did not show an association between these variables of interest. Rather, this study supports previous research that there is a decrease in odds of late-stage diagnosis if female, married and carrying private insurance. [65,123,125]

In both papers, county poverty levels and county high school graduation levels were used as contextual variables to evaluate SES. These variables have been validated to assess SES but are community level, not individual level data.

[30,31] Since this analysis did not demonstrate an association between poverty or education at the county level, further research needs to be conducted with individual level data.

In a state that has received recognition for the effective expansion of the Affordable Care Act the association between private health insurance and late-stage diagnosis is intriguing. Further research needs to be conducted on the effect of providing insurance to over 500,000 uninsured Kentuckians and if decreases the rate of late-stage melanoma diagnosis. [162]

Kentucky is a rural state with high poverty, lower than average education levels and low physician density but it appears that these factors have not impacted melanoma stage of diagnosis. As the rate of melanoma continues to increase, this paper finds that Kentucky needs to focus preventative health measures towards unmarried men who are uninsured or insured with Medicaid or Medicare.

In chapter 4, the second paper hypothesized that non-standard treatment is associated with geographic region of both rural and Appalachia, decrease in physician density, increase in poverty level and decrease in education level. This analysis of early-stage melanoma lesions from 1995 to 2013 found that 40% of these cases were provided non-standard surgical treatment. Additionally, it was noted that the incidence of non-standard surgical treatment is actually increasing over time.

This paper discovered an association between non-standard treatment and the variables of interest: Appalachian geography, poverty level and physician

density. The effect of physician density is intriguing as low all-physician density increases the odds of non-standard therapy while low dermatologist density decreases the odds. At the same time, in counties of high family practice physician density if the county also had a high poverty level there was a significant increase in non-standard treatment compared to low poverty counties. This analysis indicates increasing physician density in general improves adherence to melanoma surgical treatment guidelines but that increasing specifically family practice or dermatologist density does not.

While physician and patient preference during treatment discussions is difficult to study this study lends some insight into which patients may be vulnerable. This includes patients older than 65 years with a head or neck lesion, and with unknown insurance status. Additionally, those residing in Appalachia, a county with low all-physician density or a county with high or intermediate poverty with high family practice density and high dermatologist density are susceptible.

The specific needs of the patient have priority over general guidelines so compliance with melanoma surgical guidelines is not expected to be 100% but 40% noncompliance is considered too high. Further research should be directed by a desire to improve the understanding of the factors that influence melanoma treatment decisions between the patient and physician. Policy implementation should focus on the need to increase patient access to melanoma care while educating clinicians to end the trend of increasing non-standard melanoma treatment in the state. Future research should also investigate the increasing

non-compliance of surgical guidelines and the possible association with the stable to slightly increasing mortality rate in Kentucky.

The analyses from these two papers will be beneficial for public health practitioners because this is the first attempt to evaluate individual and social factors influencing disease stage and treatment of melanoma in Kentucky.

Implications for Public Health

The role of public health is to protect the health of the entire population through assessment, policy development and assurance. Therefore, the role of public health professionals is to assess which populations are vulnerable. Vulnerable populations are often defined by their social determinants of health in which the majority of a person's health in the United States (US) is formed. The health of a population is generally recognized by the five determinants of health; biology and genetics, individual behavior, social environment, physical environment and health services. [173]

This capstone has attempted to define the vulnerable population by evaluating the effects of biology, social environment and health services on melanoma. The incidence of melanoma is increasing faster than any other preventable cancer in the US with an expected 112,000 new cases a year by 2030. [2,3] Melanoma is a unique cancer because incidence occurs in a positive social gradient, where those with higher SES have the highest incidence while those with low SES have higher rates of late-stage disease and higher mortality rates. [6]

This capstone reinforced previous papers that highlight the increased odds of late-stage melanoma in unmarried men who are uninsured or have Medicaid or Medicare. This draws attention to the complex interplay between gender, social support of marriage and access to health services. As public health professionals, our role is to direct our screening efforts toward unmarried men without private insurance. Additionally, we must push for policy changes that increase insurance coverage for this population.

Supporting preceding research, this capstone found that 40% of early-stage melanoma lesions do not receive the standard of care surgical treatment and that the incidence of non-standard treatment is on the rise. [28,130,85142,143] This disparity in melanoma treatment is a public health concern. As epidemiologists, it is our role to bring to light the factors that are influencing a population's health. The healthcare community needs to be made aware of this disparity and who is at highest risk for non-standard treatment. We must determine why those who reside in Appalachia are twice as likely to receive non-standard surgical treatment. At the same time, public health leaders need to implement policy that increases patient access to melanoma care and educates clinicians to stop this trend within the state.

Strengths and Limitations

This capstone has several strengths including that it is the first to evaluate individual and social factors influencing disease stage and treatment of melanoma in Kentucky. Also, due to the excellent cancer registry within the state, this capstone analyzed over 10,000 cases, which provided a robust sample size.

Another strength of this capstone is the novel methodology of evaluating surgical treatment adherence for early-stage disease that had not previously been evaluated in a mostly rural, impoverished and Appalachian population. While the literature on melanoma incidence and mortality is strong the information on treatment is anemic. This capstone hopes to add to this information gap.

Despite these strengths, this capstone also has limitations, presented in chapters 3 and 4. In both papers the most notable limitation is the utilization of surrogates for SES. Although, the use of aggregate measures of SES has been validated by other studies it still cannot replace individual level data. [29-31] Also, the use of physician density was used in this study and can only be considered an aggregate of patients' use of medical services. This data is cross sectional from 2006 and may not fully represent the small variations in the physician workforce from 1995 to 2013. The actual use of physician services by these patients may not be reflective of the physician density. Additionally, this analysis of physician density provides no insight into physician practice patterns or the utilization of non-physician clinicians including physician assistants and nurse practitioners.

Another important limitation is that the analysis of poverty level, education level and physician density was done by county in a state with 120 counties and this may be a too fine a breakdown of the data. Future research may better capture community level characteristics with analysis of larger geographic regions. Lastly, this study was restricted to the state of Kentucky, which may not be representative of other parts of the country.

Recommendations

Future research is needed to help public health researchers to disentangle the complex relationship between individual and social factors in melanoma diagnosis and treatment. In addition to recommendations noted above, further research should be guided by a need to better understand the variables pertaining to both the patient and physician in melanoma treatment decisions. Researchers could gather more information regarding these treatment decisions through chart review or physician and patient survey.

To improve the evaluation of physician density, it is recommended that future research also collect data on non-physician providers who directly diagnose and treat melanoma patients. Researchers may also be able to address the issue of access to care through the use of GIS mapping techniques.

Over the last few decades the mortality rate for melanoma has not improved, remaining stable nationally and slightly increasing in Kentucky. [7] To date the association between clear margins and morality rate has not been confirmed. [54] Researchers should initiate a study with long term follow up to define the effect of non-adherence to treatment guidelines on morbidity and mortality.

Lastly, in a country that has lost control of the cost of health care, future research needs to evaluate the cost of non-standard treatment and how to provide the highest quality of care to the largest number of melanoma patients.

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Make a Difference? *Jour Surg Onc.* 2015; 112: 173-178.
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Virginia L. Valentin

University of Utah
Department of Family and Preventive Medicine
Physician Assistant Studies

Date of birth: October 5, 1978
Place of birth: Portsmouth, Virginia

EDUCATION

Years	Degree	Institution (Area of Study)
1997 - 1999	R.N.	Weber State University Ogden, UT
1998 - 2001	B.S.	University of Utah (Psychology) Salt Lake City, UT
2004 - 2007	M.C.M.S.	Barry University (Physician Assistant Studies) Miami Shores, FL Masters in Clinical Medical Science and Physician Assistant Certification

PROFESSIONAL EXPERIENCE

1997 - 1999	Certified Nursing Assistant, Intermountain Health Care, Salt Lake City, UT
1999 - 2000	Licensed Practical Nurse, Intermountain Health Care, Salt Lake City, UT
2001 - 2002	Registered Nurse, LDS Hospital, Intermountain Health Care, Salt Lake City, UT
2002	Registered Nurse, Willamette Valley Cancer Center, Eugene, OR
2003 - 2005	Clinical Research Supervisor, Willamette Valley Cancer Center, Eugene, OR
2008 - 2010	Physician Assistant, Neurosurgical Associates, Lexington, KY
2010 - 2012	Physician Assistant, Markey Cancer Center, University of Kentucky, Lexington, KY
2012 – 2016	Assistant Professor, University of Kentucky College of Health Sciences, Lexington, KY
2016- current	Assistant Professor, Associate Director, University of Utah, Physician Assistant Studies, Salt Lake City, Utah

SCHOLASTIC HONORS

2006	Outstanding PA student Scholarship, award recipient, awarded by faculty to overall best physician assistant student, Master of Physician Assistant Studies, Barry University, Miami, FL
2007	Emanuel Fien Memorial Scholarship, award recipient, awarded for excellence in physical diagnosis, Master of Physician Assistant Studies, Barry University, Miami, FL
2013	*A Teacher Who Made a Difference*, Student nominated University teaching award, University of Kentucky, Lexington, KY
2016 - 2017	Breitman-Dorn Research Fellowship. Physician Assistant Foundation.

ADMINISTRATIVE EXPERIENCE

Professional Organization & Scientific Activities

2006	Member, American Academy of Physician Assistants, Student Assembly of Representatives
2007	Member, American Academy of Physician Assistants, Student Assembly of Representatives
2010 - 2012	Representative, Kentucky Academy of Physician Assistants, Central Region Representative • Developed and implemented monthly CME dinners
2010 - Present	Member, Kentucky Academy of Physician Assistants, Legislative Committee
2012 - 2014	Member, Kentucky Academy of Physician Assistants, Annual CME Committee
2012	Member, American Academy of Physician Assistants, House of Delegates for Kentucky, Toronto
2012 - 2013	President-Elect, Kentucky Academy of Physician Assistants, • Passed state legislation to eliminate 18 month supervision • Invested in new lobbying team
2013	Member, American Academy of Physician Assistants, House of Delegates for Kentucky
2013 - 2014	President, Kentucky Academy of Physician Assistants, • Passed state legislation to decrease co-signatures to 10% • Increased board and membership involvement • Began PA week statewide celebrations
2014 - Present	Member, Physician Assistant Education Association, Government Relations and External Affairs Council (GREAC)
2014 - 2015	Past President, Kentucky Academy of Physician Assistants, • Proposed state legislation to increase PA:MD ratio to 4:1 • Invested in larger management association
2015	Member, American Academy of Physician Assistants, House of Delegates for Kentucky

Symposium/Meeting Chair/Coordinator

2013	Organizer & Participant, Kentucky Academy of Physician Assistants Annual Conference, Lexington, KY
2014	Organizer & Participant, Kentucky Academy of Physician Assistants Annual Conference, Lexington, KY

PROFESSIONAL COMMUNITY ACTIVITIES

2002 - 2005	Registered Nurse Volunteer, Volunteers in Medicine Clinic, Volunteer Run Primary Care Clinic, Eugene, OR • Performed nursing duties and operated as pharmacy leader
2003	Registered Nurse Volunteer, Cascade Health Solutions, Medical Mission to Guatemala (2 weeks) • Performed nursing duties at inpatient hospital
2005	Registered Nurse Volunteer, Cascade Health Solutions, Medical Mission to Guatemala (2 weeks) • Performed nursing duties at inpatient hospital
2011 - Present	Program Coordinator, Blessings in a Backpack, Lexington, KY • Organized volunteers, coordinated monthly food shipments and weekly delivers to elementary school students • Provides food to 60 children each week to supplement nutrition for the weekend
2012	Interviewee, Louisville Business First, Interviewed and quoted for article regarding increasing role of Physician Assistants in health care in Kentucky
2012 - 2013	Physician Assistant, Kentucky Bone and Joint Surgeons, • Clinical work one day a week as a PA in orthopedic clinic
2013	Interviewee, WEKU Radio, Kentucky, interviewed as the President-elect of Kentucky Academy of Physician Assistants
2013	Interviewee, Jessamine Journal, Interviewed and quoted for article regarding Senator Buford's award as legislator of the year
2014	Interviewee, Kentucky Radio Stations, Radio interview regarding 2014 PA legislation, played on 114 radio stations in Kentucky

SERVICE AT PREVIOUS INSTITUTIONS

2011 - Present	Member, University of Kentucky, Advanced Practice Providers
2012 - 2015	Academic Advisor, University of Kentucky, • Advised students throughout their PA education • Monitored academic advancement through lock step curriculum and met with students throughout their 28 month program to discuss their progress.
2012	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Developed and implemented shadowing program for 60 PA students as two campuses
2012 - 2014	Faculty Advisor, University of Kentucky, Physician Assistant Program, Joseph Hamburg Student Society Class of 2014 • Advising position elected by PA student • Advised/attended each monthly student board meeting • Raised $2,000 for New Hope free clinic
2012 - Present	Member, University of Kentucky College of Health Sciences, Physician Assistant Studies, Admissions Committee • Developed and implemented holistic admissions with goal of increasing diversity
2012 - Present	Member, University of Kentucky College of Health Sciences, Physician Assistant Studies, Clinical Curriculum Committee
2012 - Present	Member, University of Kentucky College of Health Sciences, Physician Assistant Studies, Didactic Curriculum Committee

2012 - Present	Member, University of Kentucky College of Health Sciences, Physician Assistant Studies, Curriculum Development Committee • Analysis of current curriculum and development of new curriculum proposal
2012	Faculty Mentor, University of Kentucky College of Health Sciences, AHEC interdisciplinary event to educate high school students about roles in health care
2012	Group Facilitator, University of Kentucky College of Health Sciences, Common Reading Experience • Read and discussed Common Reading book with interdisciplinary students
2012 - Present	Faculty Mentor, University of Kentucky College of Health Sciences, • PA mentor to pre-PA students • Individually student meetings to discuss PA profession • Formal presentation at pre-PA club meetings
2012	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Developed and implemented a one-day student education track at the KAPA conference for PA students throughout the state each noted year • Hosted the 1st, 2nd, and 3rd annual KAPA Challenge Bowl
2013	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Arranged PA students to participate in PA lobbying day at capitol in Frankfort, KY
2013	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Developed and implemented shadowing program for 60 PA students as two campuses
2013 - Present	Faculty Council Member, University of Kentucky College of Health Sciences
2013	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Developed and implemented a one-day student education track at the KAPA conference for PA students throughout the state each noted year • Hosted the 1st, 2nd, and 3rd annual KAPA Challenge Bowl
2014	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Arranged PA students to participate in PA lobbying day at capitol in Frankfort, KY
2014	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies • Developed and implemented a one-day student education track at the KAPA conference for PA students throughout the state each noted year • Hosted the 1st, 2nd, and 3rd annual KAPA Challenge Bowl
2014 - Present	Physician Assistant, University of Kentucky Medical Center, Clinical work one day a week as internal medicine hospitalist PA
2015	Faculty Representative, University of Kentucky College of Health Sciences, Physician Assistant Studies

• Arranged PA students to participate in PA lobbying day at capitol in Frankfort, KY

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

2005 - Present Member, American Academy of Physician Assistants
2008 - Present Member, Kentucky Academy of Physician Assistants
2012 - Present Member, Physician Assistant Education Association
2016 - Present Member, Utah Academy of Physician Assistants

FUNDING

09/01/13 - 12/31/14
OHNEP: Integrating Oral Health with Primary Care: Engaging Students in Advanced Nursing Practice and Physician Assistant Studies
Principal Investigator: K Skaff
Direct Costs: $2,000 Total Costs: $2,000
Oral Health Nursing Education & Practice
Role: Co-Instructor

TEACHING RESPONSIBILITIES/ASSIGNMENTS

Courses Directed

2012 - 2013 Course Director, PAS 669 Internal Medicine Clerkship, Physician Assistant Studies, University of Kentucky
• 6 credit course, yearlong course, distance learning, 60 students
• Each student takes course for 8 weeks working in internal medicine gaining experience in both ambulatory and hospital settings

Fall 2012 Course Director, PAS 650 Clinical Methods, Physician Assistant Studies, University of Kentucky
• 4 credit course, 60 students on two campuses
• 3 hour lab session, three times a week
• This course is designed to teach students to perform and document a complete history and physical exam

2013 - 2014 Course Director, PAS 663 Surgery Clerkship, Physician Assistant Studies, University of Kentucky
• 3 credit course, yearlong course, distance learning, 60 students
• Each student takes course for 4 weeks working in surgical setting

Fall 2013 Course Director, PAS 650 Clinical Methods, Physician Assistant Studies, University of Kentucky
• 4 credit course, 60 students on two campuses
• 3 hour lab session, three times a week
• This course is designed to teach students to perform and document a complete history and physical exam

Spring 2014 Course Director, PAS 651 Introduction to the PA Profession, Physician Assistant Studies, University of Kentucky
• 2 credit course, 60 students on two campuses
• This course is designed to cover health care issues for the primary care physician assistant and is taught in module format: PA profession for 10 weeks and ethics for 5 weeks which is taught by a co-instructor

2014 - 2015 Course Director, PAS 669 Internal Medicine Clerkship, Physician Assistant Studies, University of Kentucky
• 6 credit course, yearlong course, distance learning, 60 students

	• Each student takes course for 8 weeks working in internal medicine gaining experience in both ambulatory and hospital settings
Fall 2014	Course Director, PAS 650 Clinical Methods, Physician Assistant Studies, University of Kentucky • 4 credit course, 60 students on two campuses • 3 hour lab session, three times a week • This course is designed to teach students to perform and document a complete history and physical exam
Spring 2015	Course Director, PAS 651, Introduction to the PA Profession, Physician Assistant Studies, University of Kentucky
Summer 2016	FPMD 6040 Introduction to Professional Issues, Physician Assistant Studies, 48 students
Summer 2016	FPMD 6023 Oncology Course, Physician Assistant Studies, 45 students
Fall 2016	FPMD 6041 Professional Issues and Cultural Competency, Physician Assistant Studies, 46 students
Fall 2016	FPMD 6051 Evidence Based Medicine Course, Physician Assistant Studies, 46 students
Fall 2016	FPMD 6011 Hematology Course, Physician Assistant Studies, 45 students

Course Lectures

Nov 2011	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky. Physician Assistant Program, *Lymphoma and Multiple Myeloma*
Apr 2012	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Lymphoma and Multiple Myeloma*
July 2012	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Anemia, Clotting and Bleeding disorders*
Sept 2012	Guest Lecturer, PAS 657: Clinical Lab Procedures, University of Kentucky, Physician Assistant Program. *Assessment of Hemostasis*
Nov 2012	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Lymphoma and Multiple Myeloma*
Dec 2012	Guest Lecturer, MLS 460: Clinical Hematology, University of Kentucky, Medical Laboratory Science Program. *Treatment of Leukocyte Disorders*
Spring 2013	Co-Instructor, PAS 656: Patient Evaluation and Management, University of Kentucky, Physician Assistant Studies. • 4 credit course, 60 students on two campuses • 3 hour lab session, meets three times a week • Course is taught in a block format with ECG, radiology and procedures
Mar 2013	Guest Lecturer, PAS 651: Introduction to the PA Profession, University of Kentucky, Physician Assistant Studies. *PA Advocacy*
Mar 2013	Guest Lecturer, PAS 651: Introduction to the PA Profession, University of Kentucky, Physician Assistant Program. *Health Care Inequalities*

Sept 2013	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Anemia, Clotting and Bleeding disorders*
Dec 2013	Guest Lecturer, MLS 460: Clinical Hematology, University of Kentucky, Medical Laboratory Science Program. *Treatment of Leukocyte Disorders*
Sept 2014	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Lymphoma and Multiple Myeloma*
Sept 2014	Guest Lecturer, PAS 654: Clinical Lecture Series I, University of Kentucky, Physician Assistant Program. *Anemia, Clotting and Bleeding disorders*
Dec 2014	Guest Lecturer, MLS 460, University of Kentucky, Clinical Hematology, Medical Laboratory Science Program. *Treatment of Leukocyte Disorders*
Spring 2015	Co-Instructor, PAS 656: Patient Evaluation and Management, University of Kentucky, Physician Assistant Studies. • 4 credit course, 60 students on two campuses • 3 hour lab session, meets three times a week • Course is taught in a block format with ECG, radiology and procedures
Spring 2016	Instructor, University of Utah. FPMD 6042 Tutorial Course, Small Group Teaching, Physician Assistant Studies, 4 students
Summer 2016	Instructor, University of Utah. FPMD 6043 Tutorial Course, Small Group Teaching, Physician Assistant Studies, 4 students
Fall 2016	Instructor, University of Utah. FPMD 6041 Tutorial Course, Small Group Teaching, Physician Assistant Studies, 4 students

Small Group Teaching

May 2012	Small Group Facilitator, PAS 610 Research Methods, Physician Assistant Program, University of Kentucky
May 2012	Small Group Facilitator, CNU 503 Applied Nutrition, Physician Assistant Program, University of Kentucky
June 2014 - Present	Small Group Facilitator, iCats Year 1, Inter-professional education program, University of Kentucky • Member of IPE program development • 2 year curriculum of IPE education including PA, PT, RN and PharmD students

Trainee Supervision

Masters

2013 - 2014	Research Supervisor, Brittany Cianelli, Physician Assistant Program, University of Kentucky. *Pain Crisis of Pediatric Sickle Cell Patients Adversely Affects Quality of Life*

Educational Lectures

Department/Division Conferences

2013	PA Advocacy, PA Program Orientation, Physician Assistant Program, University of Kentucky
2013	Physician Assistants Legislation Update, University of Kentucky Advanced Practice Providers Quarterly Meeting

2013 PA Advocacy, PA Program Orientation, Physician Assistant Program, University of Kentucky
2013 Kentucky Physician Assistants in the future health care system, Allied Health Week, University of Kentucky College of Health Sciences
2014 Physician Assistants Legislation Update, University of Kentucky Advanced Practice Providers Quarterly Meeting
2014 PA Advocacy, PA Program Orientation, Physician Assistant Program, University of Kentucky

Continuing Education

CE Courses Taught

2016 Faculty Skills 101 PANDO Workshop, Physician Assistant Educators, 30 participants, 15 hours CME

PEER-REVIEWED JOURNAL ARTICLES

1. Coombs J, **Valentin VL** (2014). Salary Differences of Male and Female PA Educators. *Journal of Physician Assistant Education*.
2. **Valentin VL**, Dehn RW, Baker MD (2016). Commentaries on health services research. *JAAPA*, *29*(2), 1-2.
3. Morgan P, Everett CM, Humeniuk KM, **Valentin VL** (2016). Physician assistant specialty choice: Distribution, salaries, and comparison with physicians. *JAAPA*, *29*(7), 46-52.

Other (Commentary/Letters/Editorials/Case Reports/Video/Film)

1. **Valentin VL** (2014). Changes in PA Certification Maintenance. *Kentucky Academy of Physician Assistants newsletter*.
2. **Valentin VL** (2014). Physician Assistant students participating in PA legislation day at the state capital. *Connection Magazine*.
3. **Valentin VL** (2014). Can PAs call Kentucky home? *Medical News* (*22*(2), p. 22).
4. Valentin, V, Young, A, Lasley-Bibbs, V (2015). 2015 Kentucky Minority Health Status Report. Kentucky Department of Public Health.

Video/Film/CD/Web/Podcast

1. **Valentin VL** (2013). State presidential appointment [Web]. University of Kentucky web publication. Available: uknow.uky.edu.
2. **Valentin VL** (2013). President Message [Web]. Kentucky Academy of Physician Assistant website. Available: http://kentuckypa.org/.

ORAL PRESENTATIONS

Meeting Presentations (Not Published Abstracts and Not Unpublished Posters)

International

2014 Taylor S, Jones M, Schuer KM, Bennett TL, **Valentin VL**, Jones M. Faculty Development in Inter-professional Education. US-Thai Consortium for the Development of Pharmacy Education, Thailand

National

2013 Coombs J, **Valentin VL**. Is There A Glass Ceiling Over Female Physician Assistant Educators? American Academy of Physician Assistants Annual Conference, Washington, DC

2013 Skaff KO, **Valentin VL**. Preparing Faculty to Teach the Oral Cancer Screen. Physician Assistant Education Association Annual Education Forum, Workshop, Memphis, TN

2013 Coombs J, **Valentin VL**. Is There A Glass Ceiling Over Female Physician Assistant Educators? Physician Assistant Education Association Annual Education Forum, Memphis, TN

2014 **Valentin VL**, Bennett TL, Jones J, Hooker R. The Kentucky Physician Assistant Workforce: 2013. American Academy of Physician Assistants Annual Conference, Boston, MA

2014 **Valentin VL**, Bennett TL, Jones J, Hooker R. The Kentucky Physician Assistant Workforce: 2013. Physician Assistant Education Association Annual Conference, Philadelphia, PA

2015 White, R, Allman, M, Mealy, K, **Valentin, VL,** DeRosa, M, Horvath, T. Fellow Advocacy Session. Physician Assistant Education Association Annual Conference, Washington, DC.

2016 **Valentin, VL,** Coombs, J, Jones, J. Where are all the Physician Assistants in the Beehive State? Physician Assistant Education Association Annual Conference, Minneapolis, MN.

2016 White, R, Allman, M, Mealy, K, **Valentin, VL,** DeRosa, M, Horvath, T. Fellow Advocacy Session. Physician Assistant Education Association Annual Conference, Minneapolis, MN.

Local/Regional

2012 **Valentin VL**, Powdrill SG. Suturing workshop for Practicing PAs. Workshop, Kentucky Academy of Physician Assistants 36th Annual Symposium, Lexington, KY

2013 **Valentin VL**. Anemia, A Review of Anemia for the PANCE/PANRE exam. Kentucky Academy of Physician Assistants 37th Annual Symposium, Lexington, KY

2013 **Valentin VL**. Patient Center Medical Home-Collaborating Physician Training Panel. Kentucky Academy of Family Physicians & Foundation Annual Meeting, Lexington, KY

2014 **Valentin VL**, Bennett TL, Jones J, Hooker R. The Kentucky Physician Assistant Workforce: 2013. Public Health Services and Systems Research Keeneland Conference, Lexington, KY

2014 **Valentin VL**. Webinar Category 1 CME: Physician Assistants-What you need to know about the profession and how the new law will impact their practice. Kentucky Academy of Family Physicians, Lexington, KY

2014 Coombs J, **Valentin VL**. Is There A Glass Ceiling Over Female Physician Assistant Educators? Women's Health Sex and Gender Research Conference Info Fair, Salt Lake City, Utah, UT

2014 **Valentin VL**, Bennett TL, Jones J, Hooker R. The Kentucky Physician Assistant Workforce: 2013. Kentucky Rural Health Association Annual Conference, Bowling Green, KY

Peer-Reviewed Presentations

National

2016 Christian, J, Chauhan, A, Anthony, L, Nee, J, Huang, B, Durbin, E, Stewart, R, **Valentin, V,** Absher, K, Vanderford, N, Arnold, S. Spatio-temporal Analysis of Large Cell Neuroendocrine Lung Cancer in Kentucky, 1995-2012. Geospatial Approaches to Cancer Control and

Population Sciences. Bethesda, MD.

OTHER SCHOLARLY ACTIVITY

2015	Chair Academy, participant, University of Kentucky • Selected by the Dean for formal training program for future or present chairs
2016 - Present	The effect of faculty and peer interventions on stress levels of physician assistant students: A multi-site study. Principle Investigator Currently investigating IRB Approval University of Utah 91844

CONTINUING EDUCATION ATTENDED

2016	Remediation: Planning for Success, Physician Assistant Education Association, Washington, DC.
2016	Leadership I Seminar: Foundations of Leadership, University of Utah

BOARD CERTIFICATIONS

02/01/2008	National Commission on Certification of Physician Assistants, Certified

Last Updated: 12/26/2016